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GOITER:
NONSURGICAL TYPES AND TREATMENT



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GOITER: NONSURGICAL TYPES AND TREATMENT

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To
MY WIFE
IN GRATEFUL APPRECIATION
OF HER INESTIMABLE ASSISTANCE IN MY WORK
AND HER UNTIRING DEVOTION
THIS BOOK
IS AFFECTIONATELY DEDICATED

PREFACE

A MONOGRAPH on goiters curable without surgery has long been needed. This does not mean that another book on *goiter* is needed. Many volumes have been published on the various types of thyroid enlargement and the details of methods of surgical treatment. Practically all goiters are regarded in these works as requiring surgical intervention; and when other measures are mentioned, they are dismissed with a literal wave of the hand indicating that, whatever else might be tried, *surgery will eventually be resorted to.*

That this is an unjust attitude to assume is obvious when we observe that (1) goiter is preventable; (2) all early goiters are curable; (3) thyroidectomy is a failure in a large percentage of cases operated upon; and (4) a large percentage of goiters surgically treated are perfectly amenable to nonoperative procedures.

In offering this volume, I hope not only to stimulate an interest in the nonsurgical aspects of goiter in contradistinction to the surgical side of the question, but also to clarify the vision of both surgeon and internist on this timely problem. I hope to assist the reader to realize that all thyroid enlargements fall not under one heading therapeutically, but under two, *surgical* and *nonsurgical*. I trust that a perusal of these pages will make clear that to mistake a surgical for a nonsurgical goiter and *vice versa* is not only to court failure in treatment, but oftentimes to risk the very life of the patient.

It is my purpose to assist the general practitioner to classify his cases into surgical and nonsurgical types, and also to indicate what methods bring about the best and promptest results in those instances obviously of nonsurgical nature. I do not claim to promulgate anything new in the nonoperative management of thyroid enlargements. My purpose is to bring to a focus and emphasize the known facts, add to these the results of my personal experience, and direct attention to the importance of individualization: these factors, combined with the whole-hearted coöperation of the patient, constitute the essential prerequisites to success. First the diagnosis, second the careful selection of measures to be employed, and third, concerted, harmonious action of medical attendant and patient;—these comprise the triad upon which success is assured.

In the preparation of these pages, the works of many representative authorities have been consulted and credit is given in the bibliography for material employed. This, combined with the results of my intensive study of diseases of the thyroid since the year 1909, with

PREFACE

observations of thousands of patients, comprises the subject-matter herein contained.

I acknowledge with thanks permission granted me by the C. V. Mosby Co., medical publishers, for the use of paragraphs from my book entitled *Exophthalmic Goiter and Its Nonsurgical Treatment*, published in 1920.

With the exception of the chapters on treatment, much of the subject-matter herein contained is modified from my articles on goiter, published in various medical journals during the past fourteen years. Among these are articles in the *New York Medical Journal*, *Medical Record*, *International Clinics*, *Endocrinology*, *American Journal of Obstetrics and Gynecology*, *American Journal of Ophthalmology*, *Journal of the American Medical Association*, *Pennsylvania Medical Journal*, *Long Island Medical Journal*, *Illinois State Medical Journal*, and the *Ohio State Medical Journal*.

I am grateful to Dr. Solomon Solis-Cohen, Professor of Clinical Medicine at the Jefferson Medical College, for encouragement in the preparation of this book. To Dr. Charles E. de M. Sajous, Professor of Applied Endocrinology at the University of Pennsylvania, I am grateful for helpful material offered in the chapter on the Pathogenesis of Exophthalmic Goiter. To Dr. Aaron Barlow I am indebted for his kind assistance in the reading of the proof.

Finally, I am indebted to my wife through whose untiring interest, invaluable suggestions, and assistance in the translation of works by foreign authors this monograph was made possible.

1633 Spruce St.,
Philadelphia, Pa.

I. B.

INTRODUCTION

THE time has come when we must recognize that where one thyroid swelling requires the knife in treatment, another requires not the surgeon's but the internist's attention. This is a question of the physiological conception of causal relationship, of diagnosis, and of openmindedness in therapeutic approach. Despite the various devices employed to classify goiter, no one has seriously attempted a *therapeutic* classification to indicate the treatment required in a given case. Generally speaking, goiter has been regarded as a neoplastic status, and as such, requiring surgery in treatment. That this generalization is erroneous is attested not only by internists, but of recent years by representative surgeons as well.¹

From the therapeutic viewpoint, thyroid enlargements may be classified into two types: (1) *Nonsurgical*, i.e., (a) simple parenchymatous hypertrophy, (b) colloid goiter, (c) puberty hyperplasia, and (d) the hyperplastic thyroid swelling of Graves' disease or exophthalmic goiter, and (2) *Surgical*, embracing adenomatous, cystic, and all other types of thyroid enlargement not classified under nonsurgical goiter. From this classification the pathologist will observe that with the exception of strumitis, malignant goiter, and diffuse adenomatosis, surgical goiters are encapsulated, while nonsurgical goiters are diffuse or unencapsulated. Just so long as a thyroid swelling is unencapsulated, it implies a physiological necessity for more thyroid hormone elsewhere in the economy, or it indicates a defensive reaction against toxins during the existence of a focal or general infection. In these instances early and properly applied treatment effects resolution of the swelling and a restoration of the thyroid gland to its normal size. Untreated, there occurs either spontaneous recovery, a persistence or increase of the swelling, or encapsulation. At all events, it is now a recognized fact that the early institution of nonoperative measures is capable of preventing or curing all goiters prior to encapsulation. In other words, encapsulation of a goiter is an indication that physiological adaptation

¹ Of the many frank expressions as to surgical fallibility I might mention the report of H. Klose and A. Hellwig (*Klin. Wehnschr.*, Berlin, 1922, 1, 1885-1889). In their report it is shown that of 167 thyroidectomized subjects, 40 percent. had either a recurrent goiter or had been operated upon again. In 20.5 percent. of these cases operation had been performed with ligation of more than two of the arteries; in 13 percent. the operation had been performed on both sides, thus proving that even the most extensive operation is no safeguard against recurrence in certain types of goiter. Innumerable reports of similar nature may be cited in corroboration of the frequency with which nonsurgical goiter is erroneously operated upon.

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has ended and a pathological reaction has begun. It is also an indication that the nonsurgical goiter has now fallen into the category of surgical goiter, and that the opportunity for nonoperative recovery is past. It is therefore evident that all pathological or surgical goiters began as physiological or nonsurgical swellings which, had they been treated at the proper time, would have been cured without surgery.

The nonhyperplastic types of nonsurgical goiters, *i.e.*, simple parenchymatous and colloid goiters, are as a rule unassociated with constitutional symptoms aside from occasional evidences of mild hypothyroidism or of symptoms referable to pressure from an undue swelling of the mass. The hyperplastic type, on the other hand, is usually less conspicuous in size but is associated with constitutional symptoms of greater or lesser severity. Puberty hyperplasia may be so mild as to appear unrecognizable at first sight, both locally and from the viewpoint of constitutional symptoms. It is the hyperplastic type of exophthalmic goiter that is associated with marked constitutional symptoms, and it is this type that especially deserves our attention in the argument against thyroidectomy. Ample, and I hope valid reasons and proof will not be wanting in the forthcoming pages to substantiate the internist's position in favor of nonoperative procedures in the treatment of exophthalmic goiter or Graves' disease.

In my work, devoted exclusively to the diagnosis and treatment of goiter, I see a large percentage of patients, especially those suffering with Graves' disease, who present one or more scars of previous thyroidectomies with a brand new goiter superimposed. The picture is often tragic, for aside from the embarrassment experienced by females in conventional garb due to consciousness of the presence of scars on the neck, the probability of perpetual invalidism and the possibility of myxedema in later life confront all thyroidectomized subjects of Graves' disease. I respect the surgeon for his low *operative* mortality rate and indeed for saving thousands of lives through thyroidectomy in properly selected cases. But patients with simple parenchymatous hypertrophy, colloid goiter, puberty hyperplasia, and more especially *exophthalmic goiter*, are instances in which nonsurgical measures constitute the only rational procedure in treatment. The proper appreciation of therapeutic discrimination in the treatment of goiter would not only avoid unnecessary scars and other more serious results, but would strengthen the position of both surgeon and internist in their relations with the laity.

To repeat, these remarks have special application to exophthalmic goiter. How can thyroidectomy,—a measure calculated merely to overcome thyroid hypersecretion, cure a disease so complex and widespread? Though hyperthyroidism is a probable factor or incident in the disease, we have ample reasons to assume that this is a defensive reaction against other toxins,—Nature's effort to protect the individual against malicious destructive agencies originating elsewhere in the body. Even were hyperthyroidism *not* a defensive reaction, still thyroidec-

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tomy is an irrational procedure, as all the other endocrines are likewise disturbed in this disease. Thus, the *ovaries* are hypoactive; the *suprarenal medulla* is hyperactive, while the *cortex* is hypoactive; the *pancreas* is hypoactive; the *thymus* is hyperactive; the *parathyroids* are probably hypoactive; and the *pituitary, spleen, liver*, and other organs are likewise in a variable state of dysfunction. The *vegetative nervous system*, too, is "out of gear,"—now the sympathetic, now the parasympathetic assuming the dominant rôle. Hence it is that thyroidectomy, though productive of apparent relief for a brief while in a percentage of patients, does not yield clinical recovery, and hence it is that properly applied nonsurgical measures directed toward overcoming all morbid physiological processes and vicious circles characterizing the syndrome are capable of effecting complete permanent recovery.

With the removal of discoverable exciting causes and the institution of a properly outlined regimen of rest, diet, drugs, and other measures, and a practical psychotherapy pervading the whole, there is a correction of physical and mental vicious circles; there is a restoration of emotional and endocrine balance; and this, without added shock, without scars, with almost no recurrences, and no mortality rate. Such a patient, having been under the guidance of the physician for a year or longer, finally becomes self-supporting, evinces a stronger grasp on life and a healthier conception of its meaning, possesses greater mental stolidity than ever, and is more than ever equipped to face the world "irreproachable and unafraid."

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GOITER:
NONSURGICAL TYPES AND TREATMENT

CHAPTER I

ANATOMY OF THE THYROID WITH PRACTICAL CONSIDERATIONS

THE thyroid gland is a typical endocrine organ, shaped somewhat like the letter U, consisting of two lateral lobes and a connecting isthmus. It weighs between a half and one and a half ounces, varying with the age, sex, race, and stature of the individual. Harisawa made a study of the size and weight of the fresh thyroid gland in 930 autopsies. He found that in males between 26 and 42 years old it weighs on an average of 17.47 gms. and in females between 20 and 33 years of age, 15.30 gms. Castaldi, from a study of nearly 300 thyroids, concludes that the absolute weight, frequency of large pyramidal lobe, accessory thyroids and other abnormalities vary directly from region to region with the prevalence of endemic struma. The thyroid has a minimum weight in proportion to stature at the time when growth in length is greatest (*i.e.*, before puberty). The maximum relative growth of the gland takes place with the onset of sexual functioning. It is largest from 40 to 60 years of age and decreases after the menopause. This observer states that while the absolute weight is less in females than in males, the weight in proportion to stature is greater in the female; growth is also completed earlier in females than in males. It is generally believed, however, that in females the thyroid is somewhat larger than in males.¹

Relations.—The apex of each lobe rests upon the ala of the thyroid cartilage; the broad end below at its juncture with the isthmus reaches the fifth or sixth tracheal ring approximately three quarters of an inch above the sternum. Ensheathed by the pretracheal layer of cervical fascia, its firm connection to the trachea explains the up and down movements of the organ with deglutition. Posteriorly each lateral lobe is in relation with the esophagus, the pharynx, the carotid sheath, the inferior thyroid artery, the recurrent laryngeal nerve, and the parathyroid glands. These structures, if injured, give rise to the numerous post-operative symptoms referable especially to the voice and to parathyroid deficiency. The middle cervical sympathetic ganglion lies just behind the thyroid. Stimulation or irritation of this ganglion through

¹ McCarrison states that in the adult the average weight of the thyroid is 36 to 50 grams in inland tracts and hilly districts, and 20 to 30 grams at the seacoast, and that, roughly speaking, it is one-third heavier in the female.

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pressure from a neoplasm of the thyroid or elsewhere, adhesions, or inflammation may give rise to symptoms, especially ocular, simulating those of Graves' disease. The inferior laryngeal nerve on the left side is in contact with the inner surface of the lateral lobe; on the right the nerve is very close to the organ.

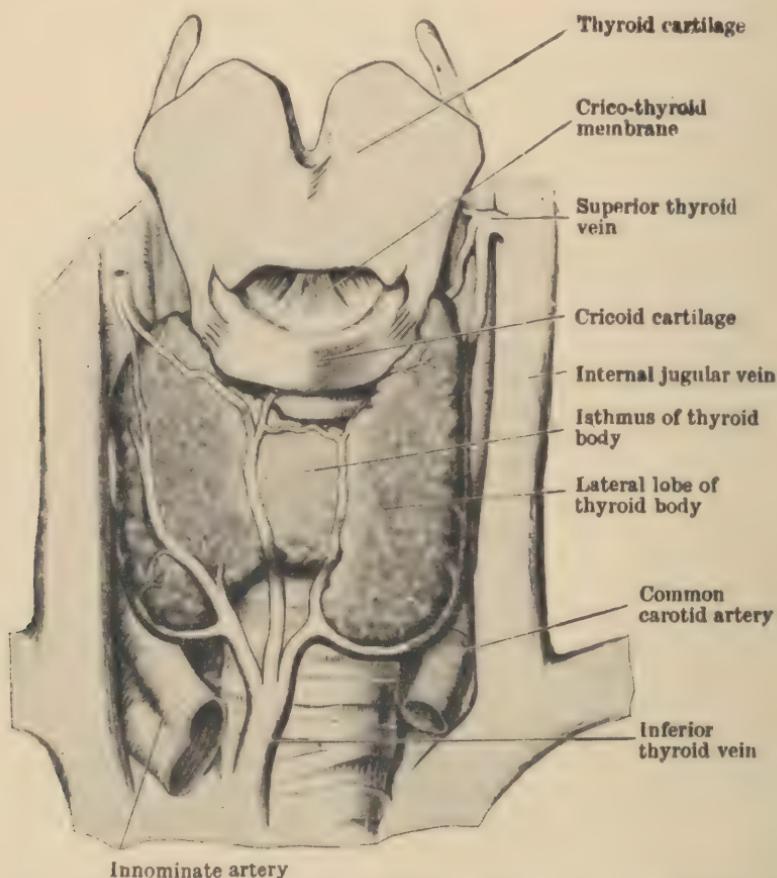


FIG. 1.—Thyroid gland and structures in immediate relation to it. (After Cunningham's Anatomy.)

The isthmus of the organ, lying over the second, third, and occasionally the fourth tracheal rings, may at times be absent, or it may give rise to a "pyramidal process." Rarely, the isthmus is so situated as to interfere seriously with an emergency superior tracheotomy. Still more rarely the isthmus is a distinct lobe, being separated from the lateral lobes.

The "pyramidal lobe," present in approximately 40 percent. of instances, and considered by most observers as the vestige of the thyroglossal duct, usually reaches and is attached to the hyoid bone. Though its base springs from the isthmus of the thyroid, it is not necessarily in the median line, being located more often closer to the left lobe than to the right.

Microscopic Structure.—The thyroid is a typical ductless gland, resembling the picture of a compound alveolar gland in structure. From the adhering connective tissue capsule, septa penetrate the body of the organ, subdividing it into lobes and lobules. From the septa, in turn, proceed finer septa forming the boundaries of terminal vesicles or alveoli. These latter are lined by a layer of cubical or columnar cells. Most of these contain colloid substance. The blood supply to the vesicles is situated in the fibrous septa; the capillaries and lymphatic vessels are just outside the vesicles.

The acini or vesicles, varying in size from 50 to 300 μ , depending upon the degree of distension by secretion, are lined with a single layer of cells, usually columnar. There is no distinct basement membrane, the cells resting upon the surrounding connective tissue. Williamson and Pearse believe the thyroid to contain a definite functional unit, of which the vesicle of the literature forms no fundamental part. The functional unit is a lymphatic sinusoid, in which the epithelium floats enmeshed in a specific plexus of capillaries. The secretion, which is not the same as colloid, is produced and stored in a specific fashion. Colloid matter is stored after another manner, and is possibly a vehicle for the carrying of some metabolite. According to Crotti, the cells forming the acini may be divided into (a) "principle" or "chief" cells which are the most numerous, containing a variable quantity of fine granules, and (b) "colloid" cells, which are somewhat more opaque and granular. These types are not in reality distinct, as one form readily merges into the other during physiological activity; the colloid cells constitute those which are loaded with material derived from the granules ready to be discharged into the lumen of the acinus. "For the majority of the thyroid cells, the secretion affects the *mecronine type*. This means that a part only of the cell is used by the secreting process. Once elaborated, the secretion is evacuated into the alveolar lumen by the breaking open of the nuclear membrane; then the cells regenerate and become 'chief cells' ready to start over the secreting cycle. In numbers of other instances, however, the secretion affects the *holocrine type*. In these cases the whole cell is used for colloid material. Nothing remains afterward, the whole cell is destroyed."—Crotti.

Blood Supply.—The thyroid gland is the most vascular organ in the body. This is why, prior to the perfection of surgical technic, thyroidectomy was the most bloody of operations. In proportion to its

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weight, the thyroid receives twenty-eight times as much blood as the head, and all the blood passes through it as it does through the brain, once every hour. It is known to be five and a half times more vascular than the kidneys. While the lymphatics are numerous, those leaving the gland are small as compared with its wonderful supply, apparent activity, and production of secretion.

Four large vessels, and occasionally a fifth, convey the blood to the thyroid body. Two superior thyroid branches spring from the external carotid arteries. Each of these divides at the apex of the lateral lobe into three branches for its supply. Two inferior branches from the thyroid axis to the subclavian artery distribute their terminal branches to the basal portions and deep surfaces of the lateral lobes. Occasionally the *thyroidea ima*, a branch of the innominate, ascends from the trachea to reach the isthmus of the thyroid body. The thyroid arteries anastomose freely with each other.

The veins which drain the blood from the thyroid body are without valves, and are still more numerous than the arteries. There are three on each side: the superior and middle thyroid veins, which join the internal jugular; and the inferior thyroid, which descends in front of the trachea and joins its fellow on the opposite side to form a large common stem which opens into the left innominate vein. Numerous large veins ramify on the surface of the organ and lie in grooves in its substance. It is from this plexus that the inferior thyroid veins take origin.

The Lymphatics.—The lymphatics begin with the organ as perifollicular lymph spaces; from these plexuses follow the interlobular septa in their course to the exterior, where they constitute a superficial plexus from which the lymph passes in all directions. Some run upward from the isthmus to small lymph nodes in front of the larynx, some from the sides to the deep glands about the internal jugular vein, and some from the isthmus and adjacent parts downward to the pretracheal lymph nodes.

The Nerve Supply.—The nerve supply is derived from the superior, middle and inferior ganglion of the cervical sympathetic, and the superior laryngeal branch of the vagus. Some observers include the inferior laryngeal nerve. The various nerve filaments are distributed to the secreting epithelium, to the walls of the blood vessels, and to the capsule and its ramifications. The secretion of the gland is under the control of the filaments from the cervical sympathetic. Cannon (quoted by McCarrison) states that as a result of experimental stimuli the secretion issues as promptly as in five to seven seconds. Cannon (see *Physiology*), in his classical experiment, has shown that when the phrenic nerve is joined to the peripheral portion of the cervical sympathetic in the cat, and the thyroid is thus continuously stimulated as the animal breathes, there result tachycardia, increased excitability, diarrhea, exophthalmos

on the operated side, great increase in metabolism, and in some cases an increase in the size of the adrenals.

Accessory Thyroids are small detached bodies consisting of tissues similar to the thyroid proper, and are occasionally found in the neighborhood of the lateral lobes or about the hyoid bone in the midline. They are sometimes found in the neighborhood of the tongue, and according to d'Aintolo (quoted by McCarrison) they may even be found under the maxilla behind the pharynx or esophagus in the region of, or more rarely in the larynx and trachea near the cricothyroid, in the vicinity of the aorta, and in the mediastinal regions. Occasionally, thyroid tissue is discovered in relation to the ovaries. Most of these are remnants of the median thyroid diverticulum from the primitive pharynx, sometimes represented by the thyroglossal duct.

Practical Remarks.—The thyroid, as a ductless gland with an internal secretion, is a vital organ, and is necessary to the growth and development of body and mind. Its congenital absence, deficiency, operative removal, or hyperactivity gives rise to cretinism, myxedema, cachexia strumipriva, and hyperthyroidism respectively,—all evidences of most marked interference in metabolic balance. The vast blood supply with the complex capillary network coming in practically direct contact with the secreting cells, the equally plentiful plexus of veins quite as closely related with these secreting units, and the copious lymph supply bathing the cells,—all these indicate that Nature intended the thyroid secretion to occupy a primal position among the body juices.

In view of the enormous blood supply, vasomotor dilatation, from whatever cause, is capable of giving rise to rapid swelling of the gland, and where there is a frequent physiologic hyperactivity with concomitant increased vascularity of the thyroid, as in numerous pregnancies, unusual types of menstruation, or repeated nervous strain, the thyroid is apt not only to remain enlarged, but to become chronically hyperactive. Again, any stimulus to the sympathetic nervous system, especially the cervical, gives rise to increased thyroid activity, and frequently repeated stimuli lead sooner or later to a chronicity of effects expressed by some of the symptoms observed in exophthalmic goiter. Irritation of the median cervical sympathetic ganglion by an enlarged simple goiter or other agency may likewise lead to a syndrome simulating that of Graves' disease. With respect to the anatomic relations, the following may be remarked:

Because of the firmness with which the sheath enveloping the thyroid attaches the organ to the surrounding structures, the gland rises and falls with the movements of the trachea. Hence all thyroid enlargements must of necessity follow the movements of the larynx.

An enlarged gland occasionally insinuates itself between the carotid artery and internal jugular vein, resulting in interference with the cir-

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culation in these vessels. If the isthmus is situated between the trachea and esophagus, this may give rise to dysphagia.

The closeness of the parathyroid glands and the recurrent laryngeal nerve must be borne in mind in the interests of good thyroid surgery.

In the events of its extreme enlargement, the ultimate relationship of the thyroid gland with the surrounding structures may result in the following symptoms:

(1) Headache, vertigo, epistaxis and cyanosis in consequence of pressure upon the carotid and jugular veins. Pressure upon the pneumogastric nerve may give rise to phenomena varying with the degree and constancy of the irritation.

(2) Dyspnea may occur in consequence of the resistance of the underlying muscles and the pretracheal cervical fascia of the gland. This symptom is most marked in instances where the isthmus is greatly involved, or where the latter is located partially or wholly behind the sternum. Occasionally, a unilateral enlargement of the thyroid gland may give rise to dyspnea by the displacement of the trachea to one side. Respiratory embarrassment may occur to extreme degree in the presence of large circular goiter constricting the trachea, or when aberrant thyroid structures within the trachea or at the root of the tongue become goitrous.

(3) Dysphagia may result from pressure upon the pharynx or the esophagus, and is more common in left-sided goiters.

(4) Dysphonias with hoarseness, and rarely aphonia may result from pressure upon the recurrent laryngeal nerve. In my experience, it has often been difficult to distinguish between the dysphonias of nerve irritation and that occasioned by the congestion due to pressure upon the upper respiratory tract. Also, symptoms of asthma may arise from tracheal pressure.

(5) Pulsation and bruit may occur in varying degree, depending upon the degree of pressure exerted upon the carotid artery by the enlarged gland and the extent of the increase in the vascularity of the organ (increase in caliber and number of blood vessels), or a combination of these factors. It is important to differentiate between the pulsations and bruit transmitted through the carotid arteries and those due to thyroid hyperplasia.

(6) Symptoms of neurasthenia and *globus hystericus* with or without hysteria may result from a goiter, usually nontoxic, as a result of moderate but persistent pressure upon the larynx or trachea.

A note of caution should be sounded with respect to local manifestations. If the patient is not young and there is pain and tenderness referable to the thyroid substance, the gland is found to be somewhat cyanotic and nodular in places, and the skin closely adherent to underlying structures, look out for malignant changes!

Accessory thyroids may become hyperactive, leading to typical

symptoms of hyperthyroidism or of Graves' disease without any perceptible enlargement of the thyroid proper. Such cases may explain some instances of Graves' disease without goiter and are frequently undiagnosed until late in the affection.

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CHAPTER II

PHYSIOLOGY OF THE THYROID GLAND

A CONSIDERATION of the most plausible facts regarding the physiology of the organ may mean either (a) a simple chemical statement regarding the manufacture of the thyroid secretion, or (b) a rather complex series of statements based upon the purpose or purposes of this secretion.

It is quite evident that the thyroid is regarded by Nature as a vital organ. The voluminous blood supply, the direct method by which the secretion enters the circulation, the manner of accumulation of the colloid, and the changes in vascularity and size of the organ during the various emergencies and epochs of life indicate that the thyroid is an important governing factor of life's processes.

The question of the importance of a secretory nerve supply to the thyroid gland is also unsettled. Although Cannon and Smith and others have emphasized the importance of controlling nerve filaments from the cervical sympathetic and the laryngeal branches of the vagus, it is also known that a variation in the blood supply of the organ is alone sufficient to account for changes of function. Moreover, chemical and biological stimulants and depressants within the blood may influence glandular secretion without the medium of nerve influences. At present, most observers believe that the degree of *vascularity* of the organ is the determining factor, as is proved by many to be the case with respect to the kidney, liver, and other organs. This is seemingly exemplified by the marked vascularity of the hypersecreting thyroid in Graves' disease.

THE THYROID SECRETION

It is probable that the hormone manufactured by the thyroid is regulated more by the blood supply than by nerve control. This is amply proved by the numerous experiments in which the thyroid tissue grafted from one animal into another resulted in successful vascularization and the assumption of function. In 1916, Manley and Marine, after making 289 autothyroid transplants in 141 rabbits, concluded that autotransplants "take" and grow, and that nerves are not essential to normal growth or functional activity of the thyroid. Krummer, in 1917, thus sums up this question: "Whatever may be the importance of the rôle played by the autonomic nervous system as the secretomotor nervous regulator of the thyroid body, the thyroparathyroid

graft without any nervous connection is capable of furnishing the internal secretion which suffices to maintain health in both the dog and the cat. From a practical point of view attempts to enervate grafts are wanting in interest. Judging from the well-known fact of the interchangeability of thyroid extracts of man and of certain animals, what we have found in the dog and the cat has every good reason to be true in man."

Colloid is the iodin-containing substance of the thyroid gland and is the vehicle in which the thyroid hormone is contained. During active secretion, especially when an emergency demand is made, as in menstruation, pregnancy, emotional disturbances, and the infections, the thyroid secretion is thrown into the blood in greater quantities. At this time, there is an increased vascularity of the gland, and a gradual thinning and entrance of the colloid substance into the lymph spaces. When the emergency need is satisfied, the gland soon reaches the "resting" stage by the reaccumulation of colloid substance within its acini. McCarrison rightly insists that a distinction should be drawn between the thyroid secretion and the colloid: "the latter term ought to be restricted to the reserve store of iodin-containing material. It is necessary to realize that the stored-up colloid is no measure of the activity of the gland at the time of its examination. This activity is indicated by the degree of parenchyma hyperplasia and the amount of 'secretion' lying between the cells and in the lymph spaces."

The amount of colloid found in a thyroid gland is in inverse proportion to the amount of thyroid secretion thrown into the blood, and usually in inverse proportion to the degree of activity of the organ. In Graves' disease, in the infections and other conditions where an increased demand for thyroid substance is made, there is diminished colloid substance in the gland; this is due to a tremendously increased absorption of the thyroid secretion, in spite of the increased secretion by the organ. In other words, in the presence of an increased demand, there is an increase in the vascularity of the gland, an increase in secretion, a greatly increased absorption of thyroid secretion into the blood, *but a diminished retention within the organ.* So that, in exophthalmic goiter, although there is an increased output of the thyroid secretion from the gland, the reservoir capacity of the organ is reduced.

In addition to iodin in the peculiar combination represented by the thyroid hormone, colloid contains phosphorus, sulphur, arsenic, bromine and various miscellaneous substances such as leucomains, cholin, lipooids, albumosis, xanthin, hypoxanthin, sodium chloride, calcium oxalate, lactic acid and other products apparently playing a minor rôle in physiological chemistry.

Iodin Content.—That iodin is a normal constituent of the thyroid has been known for many years. It is also a generally accepted fact that all thyroid products depend for their activity upon their iodin

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content. If it is true that every cell of the body depends for its proper metabolic activity upon thyroid secretion, and since this secretion depends for its activity upon the contained iodin, then every cell, every tissue, every organ of the body contains iodin. The quantity of iodin possessed by the various structures depends upon many factors. The parathyroids contain the most, the thyroid next, and the other tissues of the body come next in order. Generally speaking, the iodin content of the normal gland is the greatest, that of the colloid gland is less, the parenchymatous hypertrophic and hyperplastic gland containing the least. Each respectively contains approximately 2.5 mg., 1.5 mg., and 0.5 mg. of iodin per gram weight of dried gland.

According to Marine, a fall of the iodin content of the thyroid to below .1 percent. leads to goiter formation.

In the fetal thyroid iodin is present in very small amounts, or it may be absent. In pregnancy the iodin content of the thyroid diminishes as the time of parturition approaches, unless the mother is fed iodin, which increases it in both the maternal and fetal thyroid (Marine).

Iodin content of the thyroid increases with an increase in iodin-containing food. Thus, in a vegetable dietary and in herbivorous animals, the iodin content is greater than in a flesh-containing dietary and in carnivorous animals. Depending upon geographical conditions and dietetic habits, race likewise appears to influence the iodin content of the thyroid. Fukushima, for instance, remarks that while the total weight of the thyroid of the Japanese is one-third that of the European, Japanese thyroids contain remarkably larger amounts of iodin, probably because of the rich fish diet.

Seidel and Fenger state that in the sheep, ox, and hog, there is a marked seasonal variation in the size of the thyroid and the iodin content; there exists about three times as much iodin in the thyroid between the months of June and November as between the months of December and May. "The glands were found to be larger in the months during which the lower iodin content was noticed."

Sex and age also influence the iodin content of the thyroid; in the female, the percentage is greater than in the male, in the extremes of age the iodin content is lower than in middle life.

Residence seems to exert an influence on the iodin content; McCarrison states that the functional activity of the gland seems to increase with residence at increasing heights above the sea level.

The variations in functional activity of the thyroid in the normal experiences of human beings, *e.g.*, adolescence, menstruation, pregnancy, lactation, menopause, infections, and the various emotions,—all these bring about a variation in the iodin content of the thyroid.

Iodothyryin.—In 1895, Bauman discovered that the iodin associated with the thyroid secretion exists in organic combination which he called iodothyryin. It contains about 9 percent. of iodin and is the result of

decomposition of the proteins with sulphuric acid. The iodothyroin so obtained is about 4 percent. of the total weight of the dried thyroid.

Iodothyroglobulin.—In 1915, Oswald reported on the effect of the iodothyroglobulin on the circulation. It produces no alteration in blood pressure or pulse rate, but after intravenous injections of this substance, which Oswald calls the true secretory production of the thyroid, adrenin causes a rise in pressure which may be twice as high as before. This effect is manifest, however, only after a short latent period and persists for a considerable time, having been demonstrated after the lapse of one and a half hours.

Thyroxin.—In 1914, at the Rochester Clinic, Kendall succeeded in separating what he termed *thyroxin* from the thyroid gland. This he accomplished by destroying the proteins of the thyroid by means of boiling with a strong alkali which does not decompose the iodin-containing compound. By suitable treatment, he separated a pure, crystalline substance containing over 60 percent. of iodin, its formula being $C_{11}H_{10}O_3NI_3$. It required eight years of practically continuous investigation and more than two tons of thyroid glands to complete the process of isolating this substance. The action of thyroxin is thus described by Kendall: "When injected subcutaneously in animals, there is at first no effect on either the pulse rate or the blood pressure. After from 24 to 36 hours the dog appears restless, has a slight increase in temperature, and a decided increase in pulse rate. If a series of injections is given on successive days, these symptoms are aggravated, and after two or three injections they are accompanied by a distinct tremor, loss of weight, and severe diarrhea. On the fourth or fifth day of injection the pulse rate is between 200 and 300, and all the other symptoms continue with increased severity."

Thyroxin possesses all the properties of the dried thyroid gland, but it is 1000 times the strength of the latter. Kendall shows that thyroxin does not act on the nervous system directly, but on the tissue cells themselves. In other words, there is a direct intracellular effect throughout the whole body, acting as a catalytic agent, exchanging carbon dioxide for amino-acids, then returning to the thyroid without loss of iodin in a manner analogous to the intraorganic commerce of the hemoglobin. Kendall concludes, therefore, that all the effects produced by the thyroid are through its influence on metabolism, and the various clinical changes produced by thyroid secretion are due to an increase in cell activity throughout the whole body.

In 1915, Plummer, in correlating the data regarding thyroxin, formulated the following deductions:

1. Thyroxin is active directly or indirectly in the cells throughout the tissues of the body.
2. Thyroxin is an agent hastening the rate of formation of a quantum of potential energy available for transformation on excitation of the cell.

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3. Hyperthyroidism is the physiologic status of an individual otherwise normal when the thyroxin in the tissues is sufficient to hold the basal metabolism above normal.
4. Hypothyroidism is the opposite of hyperthyroidism.
5. All the phenomena in pure hyperthyroidism are those that most attend a sustained elevation of the basal metabolism.
6. The status of the hyperfunctionating adenomatous goiter is the result of a pure hyperthyroidism.
7. The status of exophthalmic goiter is not accounted for by a pure hyperthyroidism.

With regard to the administration of thyroxin, Plummer's deductions are exceedingly valuable to the clinician:

1. After the administration of a single dose of thyroxin sufficient to bring the basal metabolism to normal, the physiologic status of a thyroidless patient becomes normal in from ten to twelve days, remains approximately normal for ten days, and returns to the preexisting status in from five to seven weeks.
2. The amount of thyroxin in the tissues (exclusive of the thyroid) of the average normal man is approximately 14 mg. Kendall, from an analysis of the iodin content in the tissues, recently estimated the amount to be 14 mg.
3. The average daily exhaustion of thyroxin in the tissues is between 0.50 and 1 mg.
4. A shift of 1 mg. of thyroxin in the tissues of the body is accompanied by a corresponding rise or fall of between 2 and 3 percent. in the basal metabolism.
5. Fourteen milligrams of thyroxin given to a thyroidless person is not fully exhausted until from the end of the fifth to the eighth week.

Finally, we might state the facts of thyroid secretion as follows:

The thyroid gland derives its iodin from substances ingested by the individual. This iodin is stored in the colloid of the organ, as iodothyroglobulin. The tryptophane in the blood (the result of protein digestion and the action of the intestinal flora) converts the iodothyroglobulin into thyroxin, which, as such, is discharged into the circulation.

Though thyroxin is by far the most valuable substance yet isolated from the thyroid, there is increasing evidence to indicate that it is not the last word in thyroid hormone. This is attested by the work of Hunt, Miura, Hektoen, Carlson and Schulhof, and others. In my own observations I find that thyroxin is capable of bringing about violent reactions in persons requiring thyroid extract, and that it is less valuable in therapeutics than is whole thyroid gland or thyroid extract. There is still an undiscovered "something" in this organ which is of vital importance when thyroid ootherapy is indicated.

FUNCTIONS OF THE THYROID GLAND

From a biochemical viewpoint, we might state that the thyroid has but one function—that of extracting and storing iodin, manufacturing thyroxin and supplying the bodily tissues with this hormone. From a

broad physiological viewpoint, however, the thyroid gland *through its thyroxin*, is responsible for many if not most of the activities of the organism. Briefly, to sum up the purposes of the thyroid and its hormone, we might state that the organ is concerned with (1) metabolism, (2) detoxication, (3) interglandular equilibrium, (4) circulation, and (5) intellectual and emotional stability.

1. Metabolism.—Marine has well said that "Physiologically, the lung has to do with external respiration, while the thyroid has to do in some important way with internal respiration or the utilization of oxygen by the tissues." As a regulator of metabolism in its constructive and destructive phases, the thyroid plays the leading rôle. When the organ is normally at work, cellular anabolism and catabolism are maintained at an equilibrium whereby the weight of the individual is maintained at its standard, and the ideal basal metabolism, so called, is normal or zero. A deficiency of thyroid substance diminishes and an excess increases basal metabolism. Thus, in hypothyroidism the catabolic process is diminished, hence the basal metabolism may be from — 15 to — 40 or more, while in hyperthyroidism catabolism is increased and the calorimeter indicates anywhere from +15 to +100 or more. In congenital absence of the thyroid gland (cretinism), the chief features are perpetual infancy of body and mind. The body never attains maturity of growth; the neck is thick, the face large, lips thick, tongue bulky, skin dry and puffy, hair coarse and scanty, the limbs short, the abdomen prominent. The mental processes do not develop beyond the point of idiocy. There is mental torpor, a diminution of cutaneous sensibility and reflexes, lack of osseous, tendinous and muscular tonus, so that these patients sleep most of the time. Movements are slow, bones are undeveloped, umbilical and other hernias are common, feces and urine are not properly retained, and the temperature is subnormal. Acquired deficiency or absence of thyroid secretion (myxedema or cachexia strumipriva) occurring after total thyroidectomy or following disease, partakes largely of the above characteristics, excepting that the subject has already attained adult size. There is a gradual failing in the mental processes, slow, monotonous speech, poor memory, irritability, melancholia, hallucinations, and drowsiness. Tetany is an occasional accompaniment. Movement is slow and uncertain; reflexes are weak. The subcutaneous tissues become infiltrated with a mucinous substance, causing the skin to become swollen; this swelling is firm and does not pit on pressure; there is no perspiration, the skin becoming dry, rough and scaly, and assuming a yellowish-white tint. The hair is dry, scanty, and brittle, including the eyelashes and eyebrows; the nails are striated and easily broken. The features are quite characteristic, the face becoming coarse and broad, the lips thick, nostrils dilated, mouth large, and the tongue heavy. Here also the temperature is commonly subnormal. Albuminuria is the rule, and occasionally

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casts may be found. There is also constipation. Slow heart is characteristic. The elimination of disintegrated material is hindered and incomplete, and a large quantity of it is deposited in and about the various cells of the body, especially beneath the skin.

It is seen that in the presence of a deficiency or absence of thyroid hormones, the metabolic balance of every cell in the body is disturbed; broken-down cell material is retained in the form of an infiltration of mucinous subcutaneous deposits; there is a hindrance of metabolic processes, which not only deters the individual's growth of body and mind, but retards also the heat-producing forces which depend upon proper oxidization of the tissues. Even wound healing is delayed when there



FIG. 2.—Myxedema with goiter. Basal metabolism — 26.



FIG. 3.—Exophthalmic goiter. Basal metabolism + 52.

is a deficiency of thyroid. Parhon and Savini, for instance, have shown that cicatrization in thyroidectomized guinea pigs is delayed more than in test animals which have been similarly wounded but not thyroidectomized.

That cretinism and myxedema are conditions largely responsive to thyroid therapy has been known for many years. While Schiff was the first to attempt to combat thyroid deficiency by transplantation experiments in dogs in 1859, it remained for Reverdin and Kocher, in 1882, to publish their observations in patients from whom the thyroid has been removed, and thus call the attention of the medical world to the importance of the gland. Within a few years it was recognized that the underlying cause of cachexia strumipriva, sporadic and endemic cretinism and myxedema, was the same in all, *viz.*, the deficiency or ab-

sence of the thyroid. Following the suggestion of Sir Victor Horsley that myxedema, cretinism and cachexia strumipriva might be benefited by grafting a portion of healthy thyroid gland in persons suffering from these diseases, an actually successful graft seems to have been accomplished by Bettencourt and Serrano in 1890. Encouraged by this experiment, Murray, in 1891, treated the first case of myxedema with thyroid extract. The patient was a married woman of 46 who had been suffering with myxedema of several years' standing. The patient lived to the age of 74, when she died of cardiac failure. It is interesting to quote Murray's own description of the case: "The experimental nature of the treatment was explained, and the patient, realizing the otherwise hopeless outlook, promptly consented to its trial. In order to insure that the extract was properly prepared, the thyroid gland was removed from a freshly killed sheep with sterilized instruments and conveyed at once in a sterilized bottle to the laboratory where the glycerin extract was prepared. . . . A hypodermic injection of 25 minims was given twice a week at first, and later on at longer intervals. The patient steadily improved. . . . This patient was thus enabled, by the regular and continued used of thyroid extract, to live in good health for over 28 years after she had reached an advanced stage of myxedema. During this period she consumed over nine pints of liquid thyroid extract or its equivalent, prepared from the thyroid glands of more than 870 sheep."

Kendall points out that if the thyroid gland is completely removed, the basal metabolism drops only 40 percent below the average normal, where it remains substantially constant. The question as to what keeps the basal metabolism up to this level instead of dropping to zero, considerably short of which would be death, is discussed by Kendall. While it is not fully understood, he believes that amino-acids, proteins, creatin, creatinin, and probably other substances, play an important rôle in the stimulation and regulation of the basal metabolic rate. There seems to be no doubt that other members of the endocrine system play a coöperative rôle with thyroïdin, while, of course, other bodies known and unknown, with entirely different physiologic effects, may be involved. This is undoubtedly true of the suprarenals.

Rössle reports the case of a cretin of 28 in whom, on post mortem examination, no trace of thyroid could be found. The skeleton was formed as in a child of 4; there was a diminished endochondrial and periosteal ossification. Arteriosclerosis, especially of the aorta, was seen. The uterus and ovaries were as in a normal woman of 28. Only one parathyroid was found. The hypophysis was large (725 milligrams.) The thymus consisted only of fat. The pineal, pancreas and spleen were normal. The zona glomerulosa of the adrenals showed a marked sclerosis.

The quickening effect of thyroid substance on growth and metabo-

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lism has been conclusively shown by Gudernatsch in his experiments on tadpoles. He observed that tadpoles whose normal metamorphosis into frogs occupied from three to six months completed the metamorphosis in five to ten days when small quantities of thyroid substance were added one or more times to the living water of the tadpoles.

Hyperactivity of the thyroid gland with or without Graves' disease is characterized by just the reverse of the above mentioned features. The metabolism of every cell in the body is quickened. The mentality is hyperacute, the reflex hypersensitive; there is insomnia; the skin is soft, thin, moist, and erythematous; there is a progressive loss in weight; there is a tremor of the outstretched fingers and toes, and in fact an increased tonicity of all the muscular fibers of the body; there is tachycardia, often a persistent rise in temperature, chronic diarrhea, and frequently glycosuria. Here the destructive phase of metabolism is so marked that even a much greater intake of food is incapable of maintaining the body weight and strength. The metabolic determination may indicate a figure anywhere from plus 20 to plus 120 or even more.

Iseke, following a series of investigations, concludes that hyperfunction of the thyroid gland causes an increased creatin metabolism and hypofunction a lowering of the creatin output. In children up to 13, creatin, which occurs physiologically in the urine, is diminished in myxedema. This may serve as an early and differential sign by which athyreosis may be diagnosed. In exophthalmic goiter we find a high creatin content. In fevers, also, as in thyrotoxicosis, retrogressive muscular changes, and severe diabetes, excessively high creatin values appear. The excretion of creatin in the urine of children reaches its apex at about the fourth month. Then it gradually decreases and disappears from the urine at the age of 12 to 14. By noting the effect on creatin values brought about by the administration of thyroid extracts or preparations, we have an excellent means of judging their quality.

The thyroid, in unison with the pancreas (and also with the suprarenals, liver and pituitary), exerts an influence on carbohydrate metabolism. In thyroid hyposecretion the carbohydrate tolerance is increased; in hypersecretion it is diminished. This is emphasized by the constancy with which glycosuria and hyperglycemia are found in hyperthyroidism with or without Graves' disease. The question as to whether the thyroid bears any causal relationship to diabetes mellitus is still unsettled. The fact that Graves' disease is not infrequently associated with diabetes leads us to believe that perhaps such a relationship may finally be proved.

The thyroid, through its influence on cellular metabolism, exerts a regulating influence on the bodily heat. In myxedema the temperature is commonly observed to be subnormal and the skin cold, pale and dry. In hyperthyroidism the temperature is never subnormal, but often a degree or more above normal; the skin is warm, flushed and moist. The

patient commonly complains of being unable to tolerate summer weather, but finds winter quite comfortable.

To conclude, it might be stated that the effect of thyroid secretion on metabolism is somewhat similar to the relation of the fuel to a furnace. A *normal* amount of thyroid substance within the tissues keeps them in a state of poise, *i.e.*, in an equilibrium between destruction and construction whereby the individual is said to be normal in structure and function of body and mind. A *diminution* of this secretion keeps the furnace low, and we have a diminished burning down of material plus the lessened elimination of waste matter. Thus the patient's physical and mental activity is somewhere between normal and zero. An *increased* quantity of thyroid secretion creates a state of extreme firing of the bodily furnace, a quickening of all eliminative functions and marked loss in weight. It must be understood, however, that the thyroid, though the most important gland concerned in metabolism, is not the only organ controlling cellular exchange. The other endocrines, especially the suprarenals and pituitary, also play their part.

2. Detoxication.—It is the presence of iodin in the thyroid gland which seems to have given rise to the theory that the organ possesses an antitoxic, defensive and immunizing action against endogenous and exogenous poisons. On investigating the question of resistance to infection, the removal of the thyroid establishes the fact that in thyroidless animals infection is much more prevalent. The gland is looked upon, says Crookshank, as "a kind of trap or catchpit in which obnoxious material is destroyed and its elements converted to good purpose. Even so are products of waste and disintegration converted by the cells of the liver into what Glisson called 'Bile: that variously beneficial balsam of the body.'" Blum states that the thyroid neutralized in the gland itself the toxic products of intestinal origin, the enterotoxins. He believes that foods poor in iodin are the most poisonous, that those containing the most iodin are nonpoisonous and nontoxic, and that the ones saturated with iodin are harmless. Bishop and other observers conclude that the toxemia of pregnancy which expresses itself in eclampsia as its climax is due to an autointoxication from imperfect metabolism primarily caused by a failure of the organism to transform properly the waste products of the mother and fetus by the normal processes of oxidation. This in turn is believed to be the result of imperfect functional activity of the thyroid, the rational treatment of which is to supply the active principles of the thyroid secretion.

Experimental evidence emphasizes the thyroid to be an immunizing organ, protecting the body against toxins. Barbara, for instance, shows that after thyroidectomy some of the factors in immunization notably declined, including the complement, bacteriolysins, opsonic power and phagocytosis. This lowering of the defensive forces renders thyroidectomized animals more susceptible to infections. The changes in the

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thyroid commonly observed during acute and chronic infection readily explain certain symptoms observed in infections. The clinical observations and experimental pathologic physiology thus supplement and confirm each other. These data open a field for research on the effect of thyroid treatment on the serologic and cellular defensive forces in the course of infections.

The addition of thyroid extract to the treatment of syphilis, rheumatism and other infections aids greatly in the recovery of the patient. Subjects of spontaneous or induced myxedema and cretins are very prone to infections. Hunt's experiments, confirmed by Miura and others, to the effect that mice fed with desiccated thyroid are immune to acetonitrile poisoning, are an entering wedge into a most useful field in immunology. Sajous summarizes this question in the following statement: "The observations of many physiologists, pathologists and clinicians have clearly shown: (1) that removal of the thyroid apparatus reduces markedly the antitoxic and bactericidal properties of the blood, and that these properties are restored by giving thyroid gland; (2) that the blood and urine are rendered more toxic by removal of the thyroid apparatus, but that this unusual toxicity is removed by giving thyroid gland; (3) that animals are rendered more susceptible to infections by removal of their thyroid apparatus, but that they can be protected against certain toxins, particularly those capable of causing a febrile reaction, by giving thyroid gland. My own labors have indicated that this antitoxic action of the thyroid secretion was similar to that attributed by Sir Almroth E. Wright to opsonins, and also that it was a component of the systemic autotoxins or alexins; this was confirmed by several European experimenters. Fassin, Stepanoff and Marbe, Frugoni, Grixoni, and many other clinicians, including myself, have also conclusively found that thyroid medication promptly influenced favorably both autoin intoxications and infections."

3. Interglandular Equilibrium.—That the thyroid gland is strongly concerned with the maintenance of the functional balance between the endocrine and other organs of the body is attested by the accumulating evidences of physiologists throughout the world. Kendall thus sums up the relation of the thyroid to the other ductless glands in the bodily cellular changes: "While it has not been proved beyond controversy, there is much evidence to support the hypothesis that the function of the thyroid is to furnish the animal organism with ammonia resulting from the diaminization of amino-acids. The amino-group in amino-acids is unavailable for the formation of urea and other nitrogenous compounds until it has been split out of the amino-acid. This diaminization seems to be the function of the thyroid. The thyroid hormone is involved in the first split of ammonia from the amino-acids. The adrenal cortex secretion then converts this substance into some other, and the secretions of the thymus, the parathyroids, and other glands

are involved in the further elaboration of the nitrogenous constituents which finally appear in the urine. It is therefore evident that the administration of the thyroid hormone merely starts an increased rate of production of ammonia, which, in itself, does not produce hyperthyroid symptoms. It is only when the other ductless glands are stimulated that the reaction is carried on at a rate sufficient to change the basal metabolism, the irritability of the nerves, and the other effects produced by administration of the thyroid hormone. These reactions take place within the tissues and, in part, within the blood; and the speed with which they occur, and hence the equilibrium maintained, producing an increase or decrease in metabolism, depend on the stimulation of the various endocrine glands and the ability of the tissues to carry on the reactions which are made possible by the secretion from the various glands."

The relation of the thyroid to the *parathyroids* is still a matter for speculation and experimentation. In cretinism and myxedema symptoms are often observed which are directly traceable to parathyroid insufficiency. Moreover, it has been noted that tetany is improved by thyroid administration. It has also been reported that the administration of parathyroid substance, especially combined with calcium, is effectual in overcoming the tremor of hyperthyroidism. For these reasons, Gley believes that the parathyroids are part of the thyroid gland, being an embryonic and partly developed tissue. The clear-cut views previously held that the thyroid and parathyroids are opposed to each other, or that they are reciprocal, have not been supported by subsequent investigation. Vincent and Arnason, for example, have been unable to confirm the opinion that after thyroidectomy the parathyroids become hypertrophied, assuming thyroid characteristics.

The thyroid function is related to the *pituitary* in that the latter is seen to undergo extensive increase in size in thyroid disease, especially cretinism and myxedema. Ragowitsch, in 1889, observed that the pituitary becomes hypertrophied following thyroidectomy. This has been confirmed by many other observers, notably Kamo, who reports that the enlargement is more manifest in the anterior lobe of the pituitary. Trautman, experimenting on goats, and Larson, on rats, have been able to confirm these findings. Brown showed that stimulation of the sympathetic stimulates the secretion of the thyroid, pituitary and adrenal glands. Finally, the administration of pituitary extract, especially of the posterior lobe, in exophthalmic goiter, yields success in many instances.

The function of the thyroid includes a relationship with the *suprarenal* glands. This is amply illustrated not only by the influence exerted by the results of the administration of extract of suprarenal gland in a percentage of cases of Graves' disease but also by the presence in the clinical picture of this disease of areas of pigmentation not unlike

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those seen in Addison's disease. Indeed, occasional instances have arisen, where, in the presence of universally distributed pigmentation of the skin and mucous membranes, it is difficult to differentiate between Graves' disease and Addison's disease. Ott and Scott have reported that intravenous injections of thyroid extract increase the adrenin in the blood of animals. Hoskins, just prior to this, showed that the administration of thyroid substance to new-born guinea pigs produced hypertrophy of the adrenals. Pregnant adult pigs, similarly fed, however, gave birth to young in which the average weight of the adrenals was below normal. These apparently paradoxical observations were explained by the suggestion that the blood of the mother, overladen with adrenal hormones, had inhibited the growth of the fetal adrenals. Herring later showed that the administration of raw ox thyroid in large doses to cats increased the amount of adrenin in the adrenals. The weight of the adrenals was found to be increased. This observer later showed that the administration of small doses of thyroid gland to white rats produces hypertrophy of the cortex and medulla of the glands, with increase of the adrenin content. The hypertrophy of the cortex was found to be somewhat greater than that of the medulla. Accessory suprarenal tissues were also found to undergo enlargement. These observations seem somewhat confusing when we observe that Gley in 1914 and Carlson in 1916 found enlargement of the suprarenal gland following thyroidectomy. Cannon, in commenting upon these facts, remarks: "Certainly in the presence of these complexities one has no idea of thyroid influence on suprarenal function." Macleod, too, believes that no proof exists to indicate any definite relationship between the thyroid and suprarenals. My clinical observations indicate, however, that in Graves' disease the suprarenal medulla is hyperactive, while the cortex is hypoactive.

The interrelationship of the thyroid with the *thymus* gland has given rise to considerable speculation, in that a large number of patients with a hyperplastic thyroid seem to possess a coexisting hyperplasia of the thymus gland. In this relation the remarks of E. R. Hoskins are significant: "'Hyperactivity' of the thymus is frequently described where percussion indicates a dullness in the region of the sternum or a shadow is shown there by x-ray. This condition is described in case of 'mors thymica' and exophthalmic goiter. As a matter of fact it is questionable without an autopsy whether such enlargement of the thymus is not due simply to an unusually large deposit of fat. Often the size of the thymus is maintained in this manner, although relatively little thymic tissue is present. Moreover, the variability of the thymus is so great that the gland often persists normally until late in life, as is disclosed by autopsies of accident cases. Anatomists make an allowance of from 100 to 700 percent in the normal weight of the thymus at different ages. . . . Melchior has pointed out that fact often disregarded, that although

an 'enlarged' thymus is frequently found in exophthalmic goiter, the symptoms are not different when the thymus is not enlarged. . . ."

Dustin and Zunc from a study of the thyroid and thymus of normal men killed in the World War state that if the weight of the thyroid is small the weight of the thymus is great, and *vice versa*. This is contrary to the observations of most pathologists. Dustin and Zunc state that there is, however, a much greater variation in the weights of the thyroid than in the weights of the thymus in different individuals. Extensively atrophied thymus glands are rare. The authors are of the opinion that atrophy of the thymus is greatly influenced by, or even depends upon, one or more thyroid hormones.

Yamanda observes that the *spleen* and thyroid are antagonistic in their remote effects on metabolism, on the strength of the finding that after removal of the thyroid, thrombin increases in bone marrow and in blood serum, but after removal of the spleen, though the marrow effect is the same, the thrombin in the serum falls.

The thyroid gland exerts an inhibitory action upon the *pancreas*, and *vice versa*. Extirpation of the thyroid gland renders the pancreas hyperactive, and contrariwise, an increased function of the thyroid gland depresses pancreatic function as evidenced by diminished carbohydrate tolerance in Graves' disease and by the fact that in myxedema large quantities of sugar may be ingested without producing glycosuria. Kojima has shown that after a week of thyroid feeding the pancreas of the rat shows typical changes; the alveoli and alveolar cells are smaller, the nuclei vary in size and staining capacity, the cytoplasm of the cells contains comparatively little zymogen, and there are many mitotic figures, indicating rapid multiplication. After an intermission in the thyroid feeding these changes disappear. However, the extreme view held by some that thyroidectomy is the rational treatment of diabetes mellitus can hardly be supported by careful clinicians. Though Fitz, in 1919, reported 39 cases of diabetes mellitus associated with hyperthyroidism, a marked curtailment of thyroid output by means of thyroidectomy and x-rays failed to influence the course of the diabetes to any satisfactory degree. The apparent paradox of a combination of myxedema and diabetes mellitus in the same patient is occasionally observed, as instanced in Fig. 2. It has been concluded by many observers that the storage of glycogen and its discharge from the *liver* is regulated by the thyroid. Kuriyama has shown that the administration of 3 to 5 gms. of desiccated thyroid of pigs administered to white rats decreased the glycogen content of the liver in three to five days, and proved that the influence of thyroid feeding on liver glycogen can be removed by omitting thyroid from the diet. Cramer and McCall conclude that the thyroid secretion produces an increased oxidation of carbohydrates. The effect is not direct, but follows its action in discharging glycogen from the liver. They distinguish an "early" stage

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(second or third day after feeding thyroid) and a "later" stage (third to sixth day). In the "early" stage there is, in addition, a formation of carbohydrates from protein and possibly also from fat, and a subsequent oxidation of carbohydrates thus formed. There is a marked rise in carbon dioxide excretion and oxygen absorption. These observers state that the action of the thyroid secretion on the glycogenic function of the liver thus lies at the root of the increased oxidation of the proteins, carbohydrates and probably fats produced by thyroid feeding.

The thyroid stimulates the *kidney* secretion, exerting a diuretic influence. This has been amply illustrated in many instances of nephritis of the parenchymatous type in which thyroid gland was administered with resulting increased output of urine and diminution or disappearance of albumin and casts. Percy, in 1913, reported brilliant results with thyroid ootherapy in advanced cases of nephritis. He urges the use of thyroid as a preliminary to operations in patients suffering with a complicating nephritis. Percy suggests that in view of the fact that the optic nerve and retinal alterations were common findings in his patients, thyroid substance will probably prove to be the most effectual means of arresting these destructive changes in the fundus of the eye. Large doses must be given in order to obtain the desired results. Phipps and others have confirmed Percy's deductions. The same effect is seen when thyroid is given in eclampsia.

Even the *gastrointestinal* secretions are stimulated through the thyroid gland. In hyperthyroidism we commonly observe an increased secretion of the intestinal mucosa with consequent diarrhea. Contrariwise, the diminished secretions of the intestines in hypothyroidism engender persistent constipation, autointoxication, and tympanitis.

That the thyroid gland and its secretion influence the growth and functions of the *sexual organs* is thoroughly established. "The connection between the thyroid and the sex organs is intimate. It is well known that the men in India can tell in a moment whether their women have been tampered with by the condition of their thyroid" (Lane). Delay in sexual development and growth is often given an impetus when thyroid is administered. The thyroid is larger in women than in men, and it is relatively larger in children than in adults. "The thyroid gland plays a very considerable part in the characteristics of the two sexes. The female is sharper-witted, more volatile, and less stable. A woman often jumps to a conclusion without any process of reasoning, but simply by intuition gets there and sticks there, and no line of reasoning will convince her that she is not right. Thyroid metabolism has much to do with this process; women of the more reasoning type have their suprarenals perhaps more developed than their thyroids, and present other masculine characteristics" (Beebe and Beveridge). Havelock Ellis asserts, as indeed has been hinted by many others, that the gland follows closely all the

variations in a woman's organism to so marked an extent that Meckel long ago remarked that the thyroid is a repetition of the uterus in the neck.

Puberty is accompanied by an increase in the thyroid substance in both sexes, which is merely compensatory to the demands of the growing developing organs for more thyroid secretion. In the female, this enlargement is more marked, often approaching goiter in size and appearance. During menstruation the thyroid is larger than before, and it is at this time that mental disturbances are apt to arise in the absence of physical and mental rest. Increase in the circumference of the neck has been considered an accompaniment of the first sexual intercourse, and it is a very ancient custom, says Ellis, to measure the neck of newly married women in order to ascertain their virginity, a custom which still prevails in the south of France. Heidenreich, quoted by Ellis, found that a similar swelling occurs in men at the commencement of sexual relations. During pregnancy, not only is the thyroid unduly full, but a typical goitrous growth not infrequently occurs, and the organ may or may not become normal in size after parturition. A certain degree of hyperactivity of the gland is probably the natural safeguard against toxemia of pregnancy, so that thyroid gland is frequently given by some clinicians with a view to prophylaxis. The irritable, whimsical pregnant woman so often encountered by obstetricians, to say nothing of occasional instances of puerperal psychosis, is thought to be a form of thyroid dysfunction, and it is often advisable to treat such cases accordingly. Albeck has observed that there is a constant relation between the cases of emesis and the size and consistency of the thyroid; women with a large and soft thyroid never have emesis during pregnancy, while women with a small, hard thyroid are subject to emesis. Again, not only is the thyroid persistently enlarged during lactation, but it has been found that where the milk is not forthcoming in sufficient quantities, the administration of thyroid extract serves as an impetus to its secretion. The menopause is often profoundly influenced by the thyroid gland, and many of its symptoms are apparently due to an alternating hypo- and hyperactivity of the organ.

The influence of castration on the thyroid is well known. Curschmann describes the case of a woman aged 40 who developed typical myxedema after castration for fibromyoma uteri. The disease was cured by thyroid tablets. Four cases are described in which the menopause was followed by myxedema. In another case myxedema developed in a woman aged 62 after ovariotomy for a cystoma. In view of the general opinion that after ovariotomy the function of the thyroid increases, these cases deserve attention.

Many of the diseases of the uterus and adnexa are intimately associated with thyroid dysfunction. In thyroid insufficiency the pelvic organs remain small and infantile; menstruation occurs rather late in

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life and is irregular and often characterized by menorrhagia. Uterine hemorrhages are occasionally the result of an alteration or lack of one or more of the hormones which control the normal uterine flow. Because of the intimate physiologic relationship of the thyroid and the gonads, von Fellenburg administered thyroid extract in a number of cases of idiopathic sterility. Conception followed in several instances. Myxedematous women are apt to be sterile. While pregnancy in mild hypothyroidism is possible, the greater the degree of thyroid lack, the lesser the likelihood of pregnancy. Also the offspring of hypothyroid women are apt to present goiter at birth. Halsted showed that puppies born of dogs from which the gland had been partly removed possessed thyroids which were from 12 to 20 times larger than normal. More recently Ukita, experimenting on rabbits, concluded that the removal of the thyroid in the rabbit greatly prolonged the period of gestation, and that the offspring were undersized, showed delayed ossification of the bones, and thyroid hypertrophy. Commenting upon these facts, an editorial in the *Journal of the A. M. A.* remarks: "These observations suggest that . . . the function of the thyroid gland may exert some influence on the duration of pregnancy (in practice). It is possible that some cases of delayed birth are due to hypothyroidism in the mother. May premature delivery be associated with the milder grades of hyperthyroidism?"

Habitual abortion is believed by some to be due in a large percentage of cases to a deficiency in the thyroid hormone; especially is this the case in the presence of obesity. The administration of thyroid extract occasionally results in cure. Dysmenorrhea, endometritis, subinvolution, and other affections of the uterus and adnexa are frequently seen in thyroid affections. Ballin and Moehlig report a series of 200 cases (100 uterine fibroids and 100 goiters) in which 53 patients or 26.5 percent. had both goiter and fibroid uterus. Among 100 cases of toxic goiter reported by Hertzler, there was dysmenorrhea in 26, displacement in 27, dysmenorrhea with displacement in 10, metrorrhagia in 4, scanty flow in 4, myoma in 3, previous pelvic operations in 8, and evidences of earlier chronic pyosalpinx in 7. Ullman, in 1910, suggested that certain goiters can be reduced in size or cured by removal of uterine fibromata. I have in my experience seen several instances of such cures. Veil describes two cases of women with normal sexual functions in whom a thyroidectomy was performed. In both cases too much of the gland was taken away, and the symptoms of myxedema developed. Menstruation became irregular, both women showed all symptoms of a true menopause, the uterus became smaller, and finally menstruation ceased. In both cases a perfect recovery was observed after administration of thyroid gland.

4. Circulation.—There is no doubt that the thyroid, by its interrelation with the pituitary body and the adrenals, assists in governing

and regulating the heart's action, the vascular tone, the viscosity of the blood, and the blood pressure. The influence of an excess of thyroid hormone on the circulation is amply illustrated during the course of hyperthyroidism or following the administration of large doses of thyroid extract. There is an acceleration of the heart rate, a lowering (occasionally a rise) of blood pressure, a varying degree of vasomotor ataxia with a tendency toward erythema, dermographia, the capillary pulse, and hyperidrosis. Coagulability is retarded, so that a simple operation may lead to dangerous hemorrhage. In the event of marked prolongation of thyrotoxemia, myocardial degeneration frequently results, with its usual sequences.

5. Intellectual and Emotional Stability.—Aside from a consideration of physical deficiency, without thyroid hormone the human being ceases to function as such, for he is no longer capable of retaining his position in society. Crile has well said: "The thyroid is not essential to life, but it is synonymous with making life worth living." Contrary to the opinion of a few enthusiasts of thyroid surgery, a normally active individual requires all the thyroid given him by Nature so that he may successfully cope with the problems of the day, and compete physically and mentally with his fellow men. The opinion that the growing child needs but one third of its thyroid and that the adult may maintain perfect health with but one sixth of the gland given him by Nature is erroneous and leads to harmful therapeutic implications. The demands made upon the thyroid gland in the growing adult, during menstruation, pregnancy, and in the infections, and the gradual atrophy which the gland undergoes during old age, are indications of the vital importance of the entire organ throughout life. In middle age especially is the thyroid gland apt to be deficient in function, often requiring thyroid ophotherapy to offset premature senility.

The thyroid has long been called by the French *la glande de l'émotion*, because of the observed thyroid changes during deviations from one's mental poise, and because of the frequency with which exophthalmic goiter is seen to follow psychic trauma. In an individual suddenly aroused to fury or anxiety, or confronted with a fearful situation in which the instinct of self-preservation dominates the moment, the heart thumps away at a tremendous rate, the breathing is hurried and shallow, the skin becomes cold and clammy, beads of perspiration stand out on the forehead, the eyes stare ahead out of their orbits, the whole frame trembles, there is often an irrepressible desire for the expulsion of rectal and bladder contents, and the individual feels a choking sensation in the neck, with a feeling that the heart is in the mouth, causing him to insert his fingers between the neck and collar in order to stretch the latter to facilitate breathing. An analysis of this state will prove it to be a typical case of exophthalmic goiter in a transient form, with the vegetative nervous system, the adrenals, pituitary, and other endocrines

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playing their part as well. There are temporary tachycardia and palpitation, diminished respiratory expansion and dyspnea, hyperidrosis, exophthalmos, tremor, tendency to diarrhea and polyuria, and fullness of the thyroid. The term "frozen fright" as applied to exophthalmic goiter is highly applicable and indicates tersely almost the entire symptomatology of the disease. No emotion is free from a concomitant physiological hyperactivity of the thyroid gland. Even joy, laughter, hilarity, and ecstasy are accompanied by an increased thyroid vascularity and function. The event of the first connubial experience, so often mentioned by the older writer as associated with thyroid enlargement, is not a state merely of organic interaction or glandular interrelationship, but here also the sexual emotions play a prominent causative part.

What is the function of the thyroid during the emotions? The features of a cretin or of a subject of myxedema are stupid and expressionless. In the event of the "figuring out" of a given situation in which quick thinking and acting are vital, *i.e.*, in case of a conflagration, a runaway, shipwreck, or an attack by a highwayman, there is little if anything "doing in the upper story," to use a popular expression. Without the thyroid, there is no cerebration, no normal adjustment between internal relations and external circumstances. The instinct of self-preservation has not that strong, impulsive, impetuous physical backing—that storm or drive of fight or flight common to the normal being.

Depending upon the individual's previous experience and mental training, the average person meets an emergency situation quickly and often better than if there were an opportunity for premeditation. The thyroid sends out its surplus of hormone, stimulating the brain cells and whipping up the circulation, so that every cell in the economy is quickly supplied with the necessary armament to back up the self-preserving instinct. If the subject takes flight, the decision is almost instantaneous, and he runs better and with more vim and strength than ever before, and only complete physical exhaustion can stop him. If he fights, he does so even against odds, not at all heeding the terrific punishment he receives. If it is necessary to jump from a burning building, this is done promptly and to a place of safety, if there be one. And if the situation requires jumping overboard from a shipwreck, he does so without hesitation and may swim to safety, even though he never swam before. However, instead of acting quickly in self-protection, a person may become momentarily paralyzed, as it were, and fail to react satisfactorily to an emergency situation. He has plenty of thyroid, but there is a sudden blocking of the mental and physical "drive" common to normal persons, and he is helpless. It is this class of reactionless individuals, persons in whom the thyroid and the associated mechanisms work tremendously to bring results but without avail, that yield our cases of Graves' disease.

Conclusions.—In the present stage of our inquiries into the rôle of the thyroid gland in health and disease, one is impressed by the apparent universal influence the organ exerts over all the vital processes of animal life. Not a cell in the body, no matter how simple or specialized, but what its integrity is directly or indirectly controlled by the thyroid; not an organ but what its structure and function are influenced by an increased or diminished activity of the thyroid. Even the elements of the blood, the secretions and excretions of the body, are altered in quality and quantity by the "whims and fancies" of the thyroid and its coöperating glands.

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CHAPTER III

DIAGNOSIS AND CLASSIFICATION OF GOITER

Definition.—A goiter may be defined as an enlargement of the thyroid gland. This term, however, implies no dividing line between a normal and a goitrous neck, *i.e.*, where the thyroid ceases to be normal and goiter begins. According to McCarrison, an increase of $\frac{3}{4}$ to 1 inch in the circumference of the neck represents a doubling of the volume of the thyroid gland, a further increase of $\frac{3}{4}$ to 1 inch a tripling, and a still further increase of $\frac{1}{2}$ to $\frac{3}{4}$ of an inch a quadrupling of the gland's volume. These figures he considers approximately correct for necks whose normal circumference is 13 to 16 inches. In females and in children it is relatively larger than in the adult male; it also varies in size with the degree of nutrition of the patient. McCarrison's figures are merely approximate. In regions where goiter is endemic, for instance, a large percentage of thyroids there regarded as normal would be considered as at least early goiter in Philadelphia. Contrariwise, a Philadelphian with beginning goiter, sojourning in a region where goiter is endemic, would probably be looked upon as a normal individual. The term goiter carries with it a degree of personal equation, and what would often be regarded as goiter by one may be looked upon as normal by another.

Measurement of Goiters.—Except in cases of extreme emaciation, a normal thyroid should be invisible on inspection. There is no definite standard of neck circumference to indicate the presence or absence of goiter. Each neck, normal or abnormal, differs from all the rest in length, thickness, shape and the amount and distribution of adipose tissue about it. Thus in one individual the normal circumference is 14 inches, in another this figure would mean the existence of a large goiter. In still another person the neck is not normal in appearance unless a 12 inch circumference is attained. In still another a 15 inch neck circumference means a normal neck—a circumference which in a 12 inch necked individual would mean a rather unsightly goiter. In brief, an adult neck without goiter may measure somewhere between $11\frac{1}{2}$ and 16 inches in circumference, depending upon emaciation, obesity, and other individual peculiarities. The average normal neck of a normally nourished female adult should show in profile a graceful, very slight curve of concavity directed posteriorly, extending downward to the slight suprasternal hollow. No part of the thyroid should be visible. On palpation the lateral lobes cannot be felt, but the isthmus

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may be detected during deglutition in persons not obese. Enlargement of the thyroid is usually detected first at the isthmus. Occasionally, in short necked individuals enlargement of the thyroid, especially if confined to the isthmus, may be unrecognizable because of its retrosternal position. Thus the neck of a person with an intrathoracic goiter may appear entirely normal on inspection, and the goiter may not be suspected for years, until unaccountable pressure symptoms lead to the proper diagnosis.

Ordinarily, inspection and palpation are the usual means of detecting goiter. I employ circumference measurement in addition. By means of a tape measure the greatest circumference of the neck is noted in inches or fractions thereof, the posterior level of the tape being placed one inch above the prominence of the seventh cervical vertebrae, the anterior level corresponding to the greatest forward protrusion of the goiter mass. Of course in patients with goiters partially or largely retrosternal in location, such circumferential measurements are useless. In the ordinary case of goiter, results of treatment may be noted by weekly or monthly measurements. As a result of treatment the normal neck is finally reached, not by a definite figure of measurement (as there is no general standard of neck circumference), but a *reduction* of the previous circumference to the figure corresponding to an absence of thyroid swelling on inspection and a normal sized isthmus on palpation.

BORDERLINE GOITERS

We must perforce recognize a degree of thyroid swelling which the average clinician cannot regard as normal, yet to which he is unwilling to apply the term goiter. These so-called borderline cases are due in most instances to the following:

- (a) The early stage of actual goiter formation.
- (b) Heredity, with or without the tendency toward further increase in size of the thyroid to definite goiter formation.
- (c) Personal peculiarity, in which, without discoverable reasons, a person's thyroid happens to be somewhat larger than that of his fellows.
- (d) Mild subthyroidism, in which the organ must remain perpetually in a moderate degree of compensatory hypertrophy.
- (e) Convalescence from acute infectious disease—a temporary compensatory swelling.
- (f) Physiological reasons, *i.e.*, the pre-menstrual state, puberty, adolescence, pregnancy, parturition, lactation, the menopause, and instances of extreme physical and mental exertion.

Since all borderline goiters are potentially obvious goiters, they must receive careful prophylactic attention. It may be categorically stated that in nearly every case of goiter, the timely institution of preventative measures during the borderline period would have averted its occurrence.

Diagnosis of Goiter.—With the exception of (1) large intrathoracic goiter, (2) accessory or anomalously placed goiter, and (3) those which are so large and indurated as to restrict the movements of the larynx and the neck itself, it might be stated that *all thyroid enlargements follow the up-and-down excursions of the larynx during deglutition*. Palpation confirms inspection, in that the mass leaves the palpating hand in following the vertical movements of the larynx during the act of swallowing.¹ I find it best to palpate with the thumbs, permitting the hypothenar portions of the hands and the fingers to rest on the patient's shoulders. If the goiter is large, the palpating thumbs, during the upward movement of the larynx, will slip directly beneath the lower limit of the mass, thus indicating that it is not entirely intrathoracic or but partially so. If on palpation there is a thrill synchronous with the cardiac cycles, the probability is that we are con-



FIG. 4.—Series of neck profiles showing gradations from normal (a) to large cystic adenoma (j). Note that (b) and (c) may be regarded as borderline goiters merging into (d), an obvious beginning goiter. There is no apparent dividing line between (a) and (d).

fronted with a hyperplastic goiter. Percussion is not practiced over the thyroid, but if done over and about the sternum, information concerning the presence or absence of an intrathoracic goiter or enlarged thymus may be revealed. Auscultation over the thyroid reveals the presence or absence of a bruit, which must be discriminated from that obtained over the vessels of the neck. Auscultation over the upper portion of the sternum further reveals the existence of undue pressure upon the trachea, in which case the respiratory sounds will be considerably roughened and harsh. Finally, especially in surgical goiters, a laryngoscopic examination and x-ray observations may serve to indicate the presence or absence of evidences of totally intrathoracic goiters not perceptible by ordinary physical examination.

Differential Diagnosis of Goiter.—There are several non-goitrous

¹ This is done while the patient is made to swallow a mouthful of water.

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conditions, which, because they are often confused with thyroid enlargements, must be differentiated from goiter. Among the most common are the following:

(a) *Cyst of the thyroglossal duct* which is to be differentiated by the fact that its usual location is in the midline of the neck between the hyoid bone and the thyroid cartilages, considerably above the upper



FIG. 5.—Method of "fishing out" a goiter which tends to dip down behind the sternum. The patient is made to swallow while the examiner's thumbs are insinuated beneath the lower border of the goiter.

limit of a goiter; moreover, the major movements of a cyst of the thyroglossal duct are lateral, rather than up and down with deglutition.

(b) *Sebaceous cysts* and *enlarged lymphatic glands* are discovered to be independent of the movements of the larynx and are easily grasped and proved to be separate and distinct from the thyroid gland.



FIG. 6.—Relative prominence of normal thyroid from general undernutrition.



FIG. 7.—A fold of fat giving the appearance of goiter.

(c) *Cysts along the anterior border of the sternocleidomastoid muscle* (originating congenitally from the thymus) are to be discriminated as in (b).



FIG. 8.—Cyst of anterior border of left sternocleidomastoid muscle simulating unilateral goiter.



FIG. 9.—Cyst of thyroglossal duct.

(d) *Relative prominence of the patient's normal thyroid from general emaciation or undernutrition*, in which the adipose tissue over the

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organ has disappeared, leaving the gland in bold relief, may give rise to *apparent* goiter, though the thyroid is normal in size.



FIG. 10.—Sarcoma of parotid, remotely simulating goiter. Note exophthalmos of eye from retraction of lids.

of an "inward goiter." The causal relationship of the subjective "ball in the throat" is easily diagnosed by means of a careful history and physical examination.

CLASSIFICATION OF GOITER

Judging from current variations and devices employed in classification of thyroid enlargements, one must conclude that the differentiation of goiter has not yet attained scientific precision. Each clinician and author has his own pet classification of goiter which varies partially or completely from all the rest. Thus, not only is the medical attendant frequently at sea regarding the type of goiter dealt with in a given case, but treatment, too, suffers a degree of indecision as a consequence. The most reliable is the pathological classification, but since this usually implies an operative procedure for diagnostic purposes, it is hardly satisfactory to the discriminating internist. The observing clinician, however, can usually separate goiters into surgical and nonsurgical varieties through sheer force of experience, so that after all, his senses, though not infallible, are practically as reliable as the pathologist's microscope, and the percentage of error committed by him is not as great as the percentage of patients erroneously operated upon.

We shall here present three forms of classification: (1) the Patho-

(e) *A fold of fat*, on the contrary, often seen in the obese, situated in the position usually occupied by a thyroid swelling, has in many instances given rise to the appearance and fear of goiter. Examination will reveal the presence of a normal thyroid just beneath the mass of adipose tissue, which latter is easily grasped by the fingers and proved to bear no relationship with the organ.

(f) *A prominent cricoid cartilage* occasionally gives rise to the idea in the mind of the patient that a goiter is developing.

(g) *A parotid sarcoma* having extended downward toward the neck, is in rare instances confused with thyroid swelling; there should be no difficulty in making a clear discrimination.

(h) *Globus hystericus* occasionally causes a patient to apply for treatment

logical, (2) the Clinical, and (3) the Therapeutic. These, however, no matter how apparently distinct, must merge into or overlap each other, with the pathological classification as the real basis.

(1) PATHOLOGICAL CLASSIFICATION OF GOITER

A. Benign

1. Parenchymatous
2. Colloid
3. Adenomatous
4. Cystic
5. Fibrous
6. Calcareous
7. Fetal adenoma
8. Dermoids
9. Teratoma
10. Mixed types of the above

B. Hyperplasia

1. Puberty hyperplasia
2. Exophthalmic goiter
3. Combinations of hyperplasia with one or more of the benign type

C. Inflammatory

1. Acute
 - (a) Purulent
 - (b) Nonpurulent
2. Chronic
 - (a) Tuberculosis
 - (b) Syphilis
 - (c) Woody thyroiditis

D. Malignant

1. Carcinoma
2. Sarcoma

E. Parasitic

1. Echinococcus cyst
2. Chagas disease

(2) THE CLINICAL CLASSIFICATION OF GOITER

A. Simple or nontoxic

1. Physiological
2. Endemic
3. Sporadic
4. Congenital
5. Acquired
6. Intrathoracic
7. Accessory goiters (lingual, intratracheal, mediastinal, ovarian)

B. Toxic goiter

1. Toxic adenoma ("Basedowified" or secondary toxic goiter, hyperthyroidism)
2. Diffuse adenomatosis (Goetsch)
3. Puberty hyperplasia
4. Exophthalmic goiter (Graves' or Basedow's disease)

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C. Malignant goiter

1. Carcinoma
2. Sarcoma

D. Thyroiditis

1. Acute purulent
2. Acute nonpurulent
3. Syphilis
4. Tuberculosis

Remark.—Any goiter classified as simple or nontoxic may in the course of time undergo toxic, malignant, or inflammatory changes.

DEFINITIONS IN CLINICAL CLASSIFICATIONS

Since the clinical discrimination is the one which most interests the practicing physician, we shall at this point define and discuss a few terms commonly employed in the above classification.

A **Simple or Nontoxic Goiter** is a thyroid enlargement without thyrotoxemia.

A **Physiological Goiter** is a simple thyroid enlargement of compensatory nature, due to demands made upon the organ by physiological conditions elsewhere in the body. Such demands may occur during pre-adolescent or adolescent life, menstruation, pregnancy, lactation, menopause, the infections and other conditions requiring an emergency supply of thyroid hormone.

An **Endemic Goiter** is a simple thyroid enlargement constantly seen in certain regions of the world, resulting from geographical conditions and probably dependent upon a deficiency of iodin in the water, air or food.

A **Sporadic Goiter** is a thyroid enlargement not due to geographical conditions.

A **Congenital Goiter** is a thyroid enlargement present in the infant at birth and is usually due to hereditary influences.

An **Acquired Goiter** is a thyroid enlargement not present at birth.

An **Intrathoracic, Retrosternal, or Substernal Goiter** is a thyroid enlargement dipping down into the thorax. These may be (a) partially intrathoracic, *i.e.*, only the lower portion of the goiter extending downward behind the sternum, or (b) completely intrathoracic, *i.e.*, no portion of the goiter visible above the suprasternal notch.

A substernal or intrathoracic goiter may not appear to exist on casual examination of the patient, or there may be a mere thickening of the isthmus on inspection, or the patient may appear to possess a large goiter, a great portion of which extends downward into the thorax. These growths, rarely hyperplastic or malignant, are usually benign neoplasms which are harmless until they assume proportions great enough to cause pressure symptoms. Occasionally, they give rise to hyperthyroidism as in the case of other adenomata.

The history of intrathoracic goiter is often significant. The patient may assert that he was a sufferer from goiter for years, and that it had disappeared or was "cured," but that dyspnea persisted and that he is obliged to assume a certain position in bed at night in order to secure comfort. Aside from their occasional toxic attributes, the symptoms of these goiters are intractable hoarseness, dyspnea, dysphagia, occasional asthmatic attacks, headache, often vertigo, epistaxis, tinnitus, impaired vision, and insomnia. Cough may resemble that due to aneurism. Moreover, cardio-vascular phenomena from pressure upon the pulmonary, vascular and nerve structures by the mass give rise to



FIG. 11.—Goiter which is almost completely intrathoracic.



FIG. 12.—Large goiter which extends partially down into the thorax.

evidences of "mechanical goiter heart." In late and exaggerated cases there may occur acute choking sensations which may become so severe as to cause sudden death from asphyxia unless an emergency tracheotomy is performed.

Physical examination of a patient with intrathoracic goiter yields important data. Inspection reveals a variable degree of cyanosis, rarely staring eyes from dyspnea, and in severe instances dilated veins about the neck and thorax, and occasionally edema of the arms. No matter how small the substernal mass, there is usually an effacement of the suprasternal notch and the presence in this locality of a resistant mass. There is also a varying degree of ptosis of the larynx and a restriction of its excursions during deglutition. Percussion yields dulness over the sternum, usually in the midline, but dulness may be lateral as well. The percussion area of the heart may be increased. On

auscultation the breath sounds over the sternum are more tubular and often weaker than normal. The heart sounds are apt to present signs of myocardial degeneration and arrhythmia as evidences of mechanical circulatory embarrassment. Endoscopic examinations of the larynx and trachea frequently reveal valuable information. X-ray examinations are of extreme service. There is a broad shadow continuous with that of the neck. Fluoroscopic observations should be made from the anterior, posterior and lateral aspects. It will be found that the mass ascends and descends during respiration and deglutition. The fact that the tumor follows the movements of the larynx is strongly confirmatory in diagnosis. Finally we must rule out in differential diagnosis such conditions as aneurism, enlarged thymus and the other miscellaneous mediastinal conditions.

An **Accessory Goiter** is an enlargement of thyroid tissue anomalously situated, *i.e.*, at the base of the tongue, within the trachea, in the mediastinal regions, in relation with the ovaries, and elsewhere. These may undergo the changes incident to simple goiter and become "Bedowified," or become primarily hyperplastic with evidences of Graves' disease, or rarely become primarily or secondarily affected with malignancy. Accessory thyroid growths are extremely rare, and when they do occur are difficult to diagnose—often even x-ray examination does not assist us materially. In a patient suffering from unmistakable evidences of Graves' disease in whom the thyroid seems entirely normal even late in the affection, the possibility of an existing hyperplastic accessory thyroid must be borne in mind.

Köhl describes in detail the removal of a lingual goiter in a young woman and compares with this all the cases he has been able to find in the literature, a total of 119 communications on the subject and 56 additional works on the pathogenesis. In 93 cases, all were in women except 10. In 74 cases the goiter was at the base of the tongue; in 5 at the root of the tongue, and in 9 it involved both the root and the base.

Only one instance of tetany is known after removal of a lingual goiter, but there have been several cases of postoperative myxedema, and the surgeon must be sure to leave enough functional thyroid tissue to prevent hypothyroidism. This is sometimes a difficult matter, as lingual goiter is liable to return if any of the tissue is left, the remainder proliferating. On the other hand, in Asch's case, the parathyroid bodies had been included in the tumor at the base of the tongue, and their loss entailed tetany. Rubeli reports a case of lingual struma which first appeared at puberty; it increased in size with menstruation, and grew much larger during a pregnancy. It reached such a size just before delivery that tracheotomy seemed imperative, but after cesarean section at term the goiter subsided to its former size. In Zehner's case, a woman of 30 developed a cystic colloid struma of the tongue following a severe fright. Lahey aptly remarks that with the point of origin of

the thyroid in mind, the course of its descent and the knowledge that the thyroglossal tract often persists from the foramen cecum to the isthmus of the thyroid, the development of masses of thyroid tissue at (1) the foramen cecum—lingual goiter; (2) within the root of the tongue—intralingual goiter; (3) in front of the larynx—prelaryngeal goiter; (4) in the normal location of the thyroid, and (5) as a retrosternal accessory goiter, is readily understood.

A **Toxic Goiter** is a thyroid enlargement with thyrotoxemia; related to the term toxic goiter are these terms:

Hyperthyroidism, Thyrotoxicosis, and Thyrotoxemia, which imply an excessive quantity of thyroid substance in the blood, due either to the manufacture of the hormone by the patient's thyroid or goiter, or to the administration of thyroid extract *per os*. Toxic goiter, an elastic term, may be subdivided into toxic adenoma, puberty hyperplasia, diffuse adenomatosis, and exophthalmic goiter or Graves' disease.

Toxic Adenoma (*hyperthyroidism, "secondary Basedow," "Basedowified" goiter, secondary toxic goiter*) is a state of thyrotoxemia or hyperthyroidism superimposed upon a long-standing simple or nontoxic goiter. Some years after the occurrence of an apparently harmless adenoma, the patient begins gradually to complain of palpitation, dyspnea, loss of weight, weakness, nervousness, restless sleep, and other phenomena of thyrotoxicosis resembling the symptoms produced from an overdose of thyroid extract. The precise cause of the assumption of thyroid hyperactivity by a previously nontoxic goiter is not yet known. But perhaps the cause could thus be stated: The normal thyroid gland beneath the adenomatous mass, compressed by the latter, is incapable of fulfilling satisfactorily the emergency needs of the body at all times. This leads to one of two results in course of time, either a development of myxedema from deficient function of the normal thyroid tissue, or the development of thyroid activity within the adenoma as a compensatory function. Adenomatous tissue being abnormal, its function would likewise be abnormal, and as a result there is a toxic oversupply of thyroid hormone thrown into the blood, with consequent symptoms of hyperthyroidism. With regard to the time of occurrence of toxicity in a patient with a goiter heretofore nontoxic, the remarks of Plummer are of service: "Patients coming under observation with nonhyperplastic toxic goiter give a history of having first noted the goiter at the average age of 22 years, and the evidence of intoxication at the average of 36.5 years. The corresponding ages for hyperplastic goiter are, respectively, 32 and 32.9 years. That nonhyperplastic goiter is noted ten years earlier in life than hyperplastic goiter, that 14½ years elapse between the appearance of nonhyperplastic goiter and the development of notable toxic symptoms, and that the constitutional symptoms were noted but a few months (between 10 and 11) later than the goiter in the patients affected with hyperplastic thyroid, is alone sufficient to

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show that we are dealing with at least two distinct pathologic and clinical groups. That one is not the sequence of the other is self-evident."

Thyroid hypersecretion, though most usually associated with thyroid adenomata, may be observed with almost any form of thyroid pathology. Omitting the question of whether or not the hyperplastic goiter of Graves' disease is in a state of hypersecretion, we might state that any form of thyroid swelling, encapsulated or otherwise, may be associated with or really be responsible for thyrotoxemia. Thus an individual not only with adenoma but with thyroid hypertrophy, colloid goiter, cystic goiter, fibrous goiter, or even with malignancy of the thyroid, may be suffering with hyperthyroidism.

The differential diagnosis between toxic adenoma and exophthalmic goiter is tabulated in the chapter on the diagnosis and differential diagnosis of exophthalmic goiter.

There is still another means by which a simple or nontoxic goiter may appear toxic. Because of its peculiar location, a nontoxic goiter may, by pressure upon the cervical sympathetic, give rise to palpitation, tachycardia, and exophthalmos. These symptoms need not depend for their causation upon a thyroid enlargement, but may also be produced by any mass or tumor in the neck or mediastinum. The symptoms in this form of "false Basedow" are easily distinguished from those of Graves' disease: in the former, there is usually a unilateral exophthalmos, unequal pupils, pallor of the cheek of the affected side, and little or no excitation of the nervous system. During the state of paralysis of the ganglia there is ptosis of the affected eyelid with a smaller palpebral fissure, myosis, redness of the ear and perspiration of the affected side of the face.

Diffuse Adenomatosis is the term applied by Goetsch to a condition clinically simulating toxic adenoma and consisting pathologically of a series of adenomatous nodules distributed throughout the thyroid, which may or may not be perceptible on inspection. Diffuse adenomatosis differs from toxic adenoma in that the latter is a relatively large encapsulated adenoma, while the former is neither large nor distinctly encapsulated.

Puberty Hyperplasia is a thyroid enlargement with evidences of mild thyro-adrenal and sympathetic stimulation, appearing as a mild or moderate neuro-endocrine dysfunction. The condition occurs as an accompaniment of or is coincident with the physiological changes of the pre-adult period. Cases of this type are to be regarded as pre-Graves' disease patients, though many individuals become spontaneously normal in the course of time.

Exophthalmic Goiter (Graves' disease, Basedow's disease, Parry's disease, primary toxic goiter, hyperplastic goiter, dysthyroidism) is a chronic, rarely an acute dysfunction of the entire chain of endocrine

organs and of the vegetative nervous system, characterized by persistent afebrile heart hurry, tremor, increased basal metabolism, loss in weight, weakness, emotionalism, dermographia, a relative immunity to cinchonism, and usually also by a swelling of the thyroid and exophthalmos.

Since enlargement of the thyroid is inconstant, not essential to diagnosis, and merely incidental to the syndrome, it appears to me that Graves' disease should not be included in the classification of goiter, but in the consideration of constitutional affections. We might state that the subject of Graves' disease with an enlarged thyroid is no more a case of goiter than is the subject of typhoid fever with enlarged spleen a case of splenomegaly. This phase of the problem is further discussed elsewhere in this work.

Malignant Goiter may mean either malignant disease of the non-goitrous thyroid or malignant changes in a previously existing goiter. The latter is by far the most common. The diagnosis of an early case of malignancy of the thyroid—the period when surgery is most productive of good—is extremely difficult. When the diagnosis is quite evident, we are dealing with an advanced and practically inoperable case. An important observation in this relation is that the goiter of Graves' disease is practically immune to malignant changes. Plummer states that the disease has never, in the experience of the Mayo clinic, developed in a distinctly and purely hyperplastic gland. This has a practical bearing in dealing with Graves' disease subjects since many of these patients are urged to an unnecessary operation because of the fear of future cancerous changes within the gland.

The incidence of malignant goiter is variously stated, and is practically impossible to compute. It is probable that 1 percent. of all nonhyperplastic goiters are or will become malignant. It usually occurs in patients past 40 years of age, though it may be observed in the twenties. The last 6 cases brought to my attention were in patients past the age of 50.

Though incipient malignancy of the thyroid is detected with difficulty, it is not difficult to distinguish between a primary nonhyperplastic thyroid and one undergoing carcinomatous changes. Usually the following is the course of events: A goiter of long standing which has been stationary in size for years, suddenly begins to grow more rapidly. Soon, usually within a few weeks, the growth becomes more resistant to palpation and adherent to the overlying skin; it is tender to the touch, and shooting pains are felt along the cervical regions upward toward the ears and downward toward the shoulders and arms. These phenomena are quite significant and should at once arouse our suspicions. The mass becomes progressively harder, the skin more swollen and infiltrated; pressure on the esophagus and trachea soon supervenes, giving rise to dysphagia, hoarseness, and distressing cough. During all this time the patient develops the characteristic facies of malignancy:

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there is marked cachexia, anemia, insomnia and restlessness. Sooner or later the patient suffers from paroxysms of choking; the pressure upon the larynx, trachea, and inferior laryngeal nerves becomes extreme, leading occasionally to nearly complete obstruction or perforation; rarely perforation into a great vessel causes fatal hemorrhage. The patient may die of dyspnea, starvation, or during a paroxysm of choking.

In occasional instances a malignant thyroid will also give rise to toxic symptoms not unlike those of toxic adenoma. The case of Tixier and Duval is an example; in this patient, a female in whom considerable metastases to the bones occurred, tachycardia and tremor were present.



FIG. 13.—Carcinoma of a partially intra-thoracic goiter in a man 67 years old.



FIG. 14.—Inoperable sarcoma of thyroid in a woman 60 years old.

For the sake of completion, we might mention a few cases of metastatic goiter from recent literature. Crotti states that cancer metastases in bones are most frequently due to thyroid cancer; a prostatic origin comes second. The skull is the most common site for thyroid cancer metastasis, then the pelvis, sternum, femur, clavicle, lower jaw, and shoulder blades. Malignant goiter does not necessarily produce hyper- or hypothyroidism. Interference with respiration and deglutition, in a patient with a goiter which has become peculiarly irregular and hard, accompanied by shooting pains, strongly suggests the presence of malignant disease. Platou reports the case of a woman of 54 from whom an ovarian tumor was removed, which showed the structure of thyroid with colloid masses. Ray reports a case of lingual goiter which measured 5 cm. in diameter and which showed "definite evidence

of carcinomatous transformation." Binnie reports a case of primary spindle cell sarcoma of the thyroid with metastasis in the intestines. Thomsen's case, though presenting no malignant changes in the thyroid at operation, showed post-operative metastases in bones, mucous membranes and heart. In Kregliger's case of sarcoma of the thyroid there had been made a clinical diagnosis of tumor of the stomach or liver; in this case there were metastases in the skin, stomach, peritoneum, both lungs, the heart, the bile ducts and the bladder. Leclerc and Masson's case is that of a man of 67 in whom a tumor had been noted for 2 years in the left costo-iliac region. It was removed, and the man made a good recovery. From macroscopic appearance it was believed to be a sarcoma, but microscopically it proved to be made up of thyroid tissue. The patient was then reexamined and a painless, goitrous tumor was found in the left sternomastoid region. Some months later intense pain developed in the operated region and in the left thigh. Almost total paraplegia of the legs with incontinence of urine and feces followed. Hughes reports the case of a girl of 13 from whom a papilliferous carcinoma of 10 months' duration was removed from the right lobe of the thyroid; some of the lymphatic glands on the right side of the neck were also involved. Schädel observed 15 malignant out of 450 goiters seen in clinics, and in his private practice he saw 4 malignant cases. Of these 19, 14 were cancer, 4 sarcoma, 1 sarcocarcinoma. Nordmann's case was that of a girl of 10 in whom there occurred carcinomatous degeneration of an accessory thyroid. Godel's case emphasizes the importance of metastatic colloid goiter. His patient was a woman of 21 from whom a colloid goiter was removed. Sixteen years later a tumor was found in the abdomen. It proved to be a colloid goiter in the liver. Some months after this operation the woman died from an embolus in the *arteria pulmonalis* after childbirth. At post-mortem examination many tumors were found in the liver; all showed the typical structure of a colloid goiter. Guth reports the pathological findings in the case of a woman, aged 39, who died of generalized tuberculosis originating in chronic pulmonary tuberculosis. The thyroid gland was much enlarged, irregular in outline, and contained adenomata in both the lateral and median lobes. Some of these adenomata were hemorrhagic, others grayish-white, others grayish-yellow on section. Metastases were confined to a few nodules in the subperitoneal tissue in the region of the neck of the gall bladder. Microscopic examination of these metastases showed well differentiated thyroid alveoli containing colloid and similar in appearance to some of the adenomas found in the thyroid gland. He refers to Jaeger's four groups of metastasizing goiters, *viz.*, (1) those in which the primary tumor and metastases are composed entirely of cancer tissue; (2) those in which the metastases showed both benign goiter tissue and cancer; (3) those in which it is difficult to determine what portion of the tumors are carcinomatous;

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and (4) those apparently benign goiters showing metastases with normal thyroid alveoli formations throughout. Finally, the case of Meleney is noteworthy in that carcinoma of the thyroid with metastasis in the cervical lymph glands occurred in a patient of 17, the tumor having existed for 6 years.

Thyroiditis is an inflammation of the thyroid gland. Related to this condition is *strumitis*, an inflammation of a previously existing goiter. The terms thyroiditis and strumitis are usually employed interchangeably.

Acute Thyroiditis may be primary, but is usually secondary to infection elsewhere or to an acute infectious disease. An attack of thyroiditis is usually heralded by chilliness, high fever, pain in the region of the thyroid spreading to the shoulders and the nape of the neck and accompanied by swelling and diffuse puffiness of the thyroid area. Dysphagia and dyspnea are variable in degree and at times alarming. If this patient is predisposed to Graves' disease there may be added persistent tachycardia, tremor, nervous excitation, exophthalmos not receding on the disappearance of the thyroid inflammation, and we may be face to face with a typical case of the syndrome. This may occur during the course or immediately following a thyroiditis of traumatic origin, or such local infections as tonsilitis and mastoiditis, or as a complication or sequel to acute articular rheumatism, typhoid fever, influenza, and the like. Suppuration in cases of acute thyroiditis is rare. Beilby, in a report of 3 cases of acute thyroiditis found the infection to occur in the normal thyroid in 2 and in a cystic adenoma in the third. In 2 of the cases the infection was a direct extension from a laryngeal and tracheal inflammation. The infecting organism was a staphylococcus.

Chronic Thyroiditis is represented by syphilitic and tuberculous infection.

Syphilitic Thyroiditis occurs more often than is observed or reported. It may appear as a gumma or as a diffuse proliferation terminating in sclerosis of the thyroid. Doubtless many of the sporadic goiter cured by the iodides are of syphilitic origin. Simonton found syphilis to be the cause of the disease of the thyroid gland in five cases.

All of these cases showed a positive Wassermann reaction and four of them received specific treatment with successful results. The author concludes that a Wassermann test should be made in all cases of tumor or disturbance in function of the thyroid before operation is resorted to.

Tuberculous Thyroiditis of follicular or caseous forms is relatively rare. The fact that subjects of phthisis frequently present an enlarged thyroid is significant. The case of Gilbert and Castaigne, quoted by Roussy, presented tubercle bacilli in the thyroid gland.

Broders reports 7 cases of tuberculosis of the thyroid which have been under observation in the Mayo clinic. They were divided into 3 groups:

(1) cases with high degree of hyperthyroidism, (2) with a moderate degree of hyperthyroidism, (3) hyperthyroidism mild or absent. In each case the diagnosis was made after the enlarged gland had been removed by operation. The greater the tuberculous involvement the less severe the toxic symptoms. Broders believes that all cases of tuberculosis of the thyroid are secondary to some focus elsewhere in the body, although none were discovered in the 7 patients. Mosiman also reports 9 cases of tuberculosis of the thyroid most of which were discovered accidentally in course of the routine microscopic examination of glands removed at operation. In all of these cases there was evidence of a primary focus of tuberculosis in some other part of the body, or a definite history of a prolonged exposure to the disease. He therefore believes that it is extremely doubtful if primary tuberculosis of the thyroid occurs. The tuberculous process was found associated with various physiological and pathological changes in the gland such as hyperplasia, pure colloid goiter, adenomatous goiters and sarcoma. Rendelman and Marker, despite the doubt of the existence of primary tuberculosis of the thyroid, nevertheless report such an instance in a woman of 22. This patient had several attacks of tonsillitis and a discharging sinus over the thyroid which showed itself at the age of 10 and healed after a year's draining. At 12 it again opened and drained for 3 years, when it healed. Nine months prior to the present observation the patient began to notice a gradual enlargement of the thyroid, appearing as a simple goiter without apparent systemic disorder. The basal metabolism was —18 and —24 on two occasions. Operation was performed; on gross examination malignancy was diagnosed. Microscopic examination revealed a diffuse noncaseating tuberculosis of the thyroid. After operation a myxedematous state developed, requiring thyroid ophotherapy.

We shall now examine the *therapeutic* classification, with which this book is mainly concerned.

(3) THERAPEUTIC CLASSIFICATION OF GOITER

A. Surgical goiter

Adenomatous, cystic and all other thyroid enlargements not classified under nonsurgical goiter

B. Nonsurgical goiter

1. Parenchymatous hypertrophy
2. Colloid goiter
3. Puberty hyperplasia
4. Hyperplasia of exophthalmic goiter (Graves' disease)

A **Surgical Goiter** is a thyroid enlargement amenable to operative treatment.

A **Nonsurgical Goiter** is a thyroid enlargement amenable to non-operative treatment. Though in nonsurgical goiters spontaneous recovery may take place in a minority of cases, if proper treatment is

ILLUSTRATIONS OF SURGICAL GOITER.



FIG. 15.—Large circular adenoma.



FIG. 16.—Toxic adenoma.



FIG. 17.—Cystic goiter.



FIG. 18.—Cystic adenoma.

delayed the great majority of cases may undergo changes requiring surgical interference. On the other hand, it may be stated of the common types of surgical goiter that there was a time in the history of each case when it was nonsurgical and curable by nonoperative measures.

In general, the following table will assist in the differentiation between the *common* surgical and the nonsurgical goiters:

Surgical Goiter.

1. Usually occurs in established adult life and thereafter.
2. Usually of at least five to twenty or more years' duration.
3. Often very large, occasionally intrathoracic, frequently asymmetrical.
4. Genuinely neoplastic and adventitious.
5. Encapsulated, except diffuse adenomatosis, infections and malignant types.
6. Resistant and often nodular to the touch; thrill rare.

7. Bruit rare.

8. Thyroidectomy is complete and satisfactory in non-malignant types.

Nonsurgical Goiter.

1. Usually occurs during childhood, preadult or early adult life.
2. Duration varies from several weeks to several years.
3. Rarely very large or intrathoracic, usually symmetrical.
4. Not genuinely neoplastic nor adventitious, but usually a compensatory reaction.
5. Not encapsulated.

6. Usually yielding and diffuse to the touch; thrill characteristic of hyperplastic type. A growing colloid goiter may offer resistance to palpation.
7. Bruit nearly always present in hyperplasia of exophthalmic goiter.
8. Thyroidectomy is fallacious and leads to recurrence.

The general attitude that surgery is the only cure for goiter leads not only to unnecessary operative risks and scars, but to a diminished confidence of the laity in the medical profession. A reaction, coming none too soon, is, however, very evident in this connection. A large percentage of surgeons are to-day refusing to operate and most up-to-date surgeons are at least hesitant to operate upon the above designated nonsurgical goiters. The time is soon to arrive when the therapeutic, rather than the pathologic classification of thyroid enlargements will be regarded not only as the most important step in diagnosis, but also as the real essential in the interests of the patient's welfare.

It is not difficult clinically to discriminate nonsurgical from surgical goiter. A careful history of the patient, with particular reference to age, heredity, sexual life, previous illnesses, focal infections, and emotional make-up, is of importance. In addition to the above tabulation, the physical examination of the mass is of assistance. The following are the salient features to be observed:

Parenchymatous Hypertrophy presents a symmetrically enlarged

ILLUSTRATIONS OF THE FOUR TYPES OF NONSURGICAL GOITER



FIG. 19.—Colloid goiter.



FIG. 20.—Parenchymatous hypertrophy.



FIG. 21.—Puberty hyperplasia.



FIG. 22.—Exophthalmic goiter.

thyroid; it may be so slight as to appear normal at first glance, but often assumes the proportions of large goiter. Between these extremes many gradations in size are seen. The thyroid is moderately yielding to the palpating fingers, resembling closely the consistency of the normal living thyroid. There is no thrill, and on auscultation no bruit is audible. This type of goiter indicates the participation of the thyroid in a physiological event in which the organ must undergo a compensatory enlargement because of demands made upon it for increased function.

Colloid goiter usually occurs during pre-adolescent years, but may also occur during childhood and early adult life. Occasionally colloid goiter is seen in middle age, in either sex, though more often in the female. Colloid goiter varies in size from the appearance of a moderate or evident fullness of the thyroid to the rather large mass disfiguring the individual. At times pressure symptoms are experienced. The growth is generally symmetrical in shape and appears to be under tension. Palpation confirms this, as the trained palpating fingers will find the mass doughy and rather resistant to the touch. As in the case of thyroid hypertrophy, there is neither thrill nor bruit in colloid goiter. This type of thyroid enlargement, too, is due to physiological demands made upon the organ, but through some mysterious reason the acini of the organ, instead of becoming multiplied as in hypertrophy, become markedly distended with colloid substance.

Puberty Hyperplasia presents a picture midway between parenchymatous hypertrophy and the hyperplastic goiter of Graves' disease. It is an exaggerated hypertrophy which is not vascular enough to produce thrill or bruit. On the advent of an exciting cause of Graves' disease, it may, with the development of the syndrome, become quite vascular, and present thrill and bruit.

Hyperplastic goiter of Graves' disease is essentially vascular. The swelling may be so trivial as to be unobserved, or it may be large enough to assume the size of a large colloid goiter. It must be remarked in passing that not all cases of exophthalmic goiter present goiter, and as a corollary, it is therefore obvious that the term exophthalmic goiter is not always scientifically consistent. Still, common usage compels us to employ this term for yet a while. Hyperplastic goiter occurs most often in early adult life, but occasionally is seen in the extremes of age. Physical examination of this type of goiter presents distinct phenomena not observed in any other form of thyroid enlargement. Though on inspection the thyroid is as symmetrical as in the other forms described, we find here on close inspection a distinct throbbing synchronous with the cardiac cycles. On palpation a thrill is distinctly evident, and moderate compression, in causing an expulsion from the mass of some of its blood, reduces its size, somewhat as one would affect this change in compressing a loaded sponge. On auscultation a distinct bruit is heard. This sound is loud, harsh in quality, always systolic but often

RESULTS OF SURGICAL TREATMENT OF NONSURGICAL GOITER.



FIG. 23.—Recurrence of colloid goiter following thyroidectomy.



FIG. 24.—Recurrence of parenchymatous hypertrophy following thyroidectomy.



FIG. 25.—Beginning recurrence of hyperplastic goiter 5 months after thyroidectomy.

RESULTS OF SURGICAL TREATMENT OF NONSURGICAL GOITER



FIG. 26.—Same patient as in Fig. 27, about 14 years before the frank manifestations of Graves' disease; note the slight exophthalmos of right eye.



FIG. 27.—Recurrence of hyperplastic goiter despite two thyroidectomies; the patient is here in state of circulatory decompensation.

diastolic as well in occurrence. The throbbing, compressibility, thrill, and bruit are pathognomonic of the hyperplastic goiter of Graves' disease.

The colloid and hyperplastic types of nonsurgical goiter may each be compared to a loaded sponge. The reduction of the colloid substance and of the vascularity respectively, in the unloading and permanent contraction of the organ by therapeutic means, is tantamount to cure. To a lesser degree this may be said of physiological hypertrophy and of puberty hyperplasia.

To summarize the remarks concerning the therapeutic classification of goiter, we might state the following:

1. The therapeutic discrimination of goiter into surgical and non-surgical types, is the most important classification in so far as the patient's interests are concerned.

2. Nonsurgical goiters are the 4 common nonencapsulated types of thyroid enlargement, *viz.*: (a) simple parenchymatous hypertrophy, (b) colloid, (c) puberty hyperplasia, and (d) hyperplastic goiter of Graves' disease. All other common types of goiter are encapsulated and surgical.

3. Surgical treatment of nonsurgical goiter is a fallacious procedure, yielding, at best, a low operative mortality rate and a neat scar. The percentage of clinical recovery is relatively negligible.

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4. Nonsurgical goiters are completely and permanently cured by nonoperative means. The conditions necessary to attain this result are *first*, the medical attendant must be reasonably certain of the diagnosis and must have ample experience in the therapeusis of goiter, and *second*, the patient must coöperate religiously in the carrying out of instructions in treatment.

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CHAPTER IV

PATHOLOGY OF NONSURGICAL GOITER

IN the discussion of the pathological findings of nonsurgical goiter we shall discuss briefly 1. simple parenchymatous hypertrophy, 2. colloid goiter, 3. puberty hyperplasia, 4. hyperplastic goiter of Graves' disease, and 5. miscellaneous pathological findings of Graves' disease.

1. SIMPLE PARENCHYMATOUS HYPERTROPHY

The pathology of the thyroid in simple parenchymatous hypertrophy is practically identical with that of mild hyperplasia, except that there is more colloid and less vascularity in the former than in the latter organ. The gland is enlarged because of physiological demands made upon it through focal infections, or through the gonadal changes of puberty, adolescence, menstruation, pregnancy or the menopause. Puberty and pregnancy are the most common causes of this form of thyroid enlargement. Simple parenchymatous hypertrophy of the thyroid is an indication that the organ is incapable of supplying sufficient hormone to the economy during periods of physiological stress. Hence, there is, so to speak, a state of temporary hypothyroidism, and because of this, the organ must undergo a parenchymatous proliferation, with concomitant increased functional capacity, so that an equilibrium between supply and demand for thyroid secretion is secured.

The organ may be but slightly increased in size, or it may enlarge to definite and at times alarming goiter formation. There is an increase in vascularity, an increased number of vesicles; there is a moderate amount of infolding of the epithelium within the vesicles, and the individual cells tend toward the cuboidal and at times the columnar type. The vesicular spaces may be normal in size, occasionally increased because of a greater amount of colloid, but in the majority of instances these spaces are smaller, and the amount of colloid is reduced. In other words, the gross and microscopic pathology of this form of goiter indicates increased parenchymatous structure.

Occasionally, such a thyroid swelling may present a combination of increased parenchyma and the architecture seen in colloid goiter. In other words, portions of the organ may present increased secreting structure and other portions decreased function because of destruction of parenchymatous cells from overdistention of the follicles with colloid

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material. Occasionally, portions of the organ may show evidences of very typical hyperplasia, and again there may be an admixture within the mass of adenomatous nodules.

It is with the unencapsulated, simple, parenchymatous, physiological enlargement that we are here concerned, a thyroid enlargement which is amenable to preventative measures and curable through non-surgical treatment if therapeusis be instituted at the proper time.

2. COLLOID GOITER

In colloid goiter the gland is considerably enlarged, rather diffuse and uniform, in the early stages conforming faithfully to the shape of the normal thyroid. Occasionally the surface of the gland may be nodular because of localized follicular distension with colloid. At times large cysts are formed which may become encapsulated. These are of variable size, occasionally assuming enormous proportions. On section the organ presents a somewhat honeycombed structure. There are large spaces filled with a brownish, gelatinous, translucent colloid material. Not infrequently there is seen a fusion of dilated vesicles forming cysts of varying size and shape.

Microscopically, the gland consists of dilated vesicles filled with colloid which, present in enormous quantities, have flattened and in some instances destroyed the lining of the epithelial cells.

3. PUBERTY HYPERPLASIA

The thyroid in so-called puberty hyperplasia presents the picture of the hyperplastic organ of Graves' disease, but in mild form. Indeed, we might state that the pathological structure of puberty hyperplasia is that midway between parenchymatous hypertrophy and the hyperplasia of Graves' disease. The gland is at times difficult to distinguish from simple physiological hypertrophy from which it differs in degree of parenchymatous proliferation, the contained colloid, and in vascularity. There is an increase in the size of the cells of the acini, some of the cells assuming the columnar form, and an attempt at alveolar infolding at the expense of the vesicular space. Moderate hyperemia is characteristic. The colloid may be normal, occasionally increased, but usually reduced in quantity.

4. PATHOLOGY OF THE THYROID IN EXOPHTHALMIC GOITER

Since Graves' disease is a condition in which, through the accelerated catabolic process and the generalized dysfunction of the entire chain of endocrine organs and of the vegetative nervous system, there is a modification of the function of every tissue and organ of the economy, it is reasonable to infer that the pathological changes, too, are wide-

spread. Let us discuss the most important pathological findings *seriatum*:

The thyroid gland in Graves' disease is essentially in a state of hyperplasia. Though macroscopic increase in the size of the organ is usually present, the increase varying from twice to many times its normal size in many exceptional instances, the organ may not be enlarged at all. Kocher and others have found hundreds of cases in which there was no increase in size of the gland. Indeed, it is occasionally observed that the organ appears a trifle smaller than normal. In Murray's series of cases, according to McCarrison, goiter was absent in 4.3 percent. In my own experience, there is usually in those instances in which goiter is absent, a slight thickening of the right lobe of the gland which at times is difficult to distinguish from the border of the sternocleidomastoid muscle, but which is tender on deep palpitation and follows the movements of deglutition. Again, it must be recalled that in the absence of visible thyroid enlargement, there is the possibility of an enlargement of an accessory thyroid.

The swelling observed in the usual case of Graves' disease is soft and diffuse, variable in size, and is made more prominent by having the patient hyperextend the neck. Because of its vascularity it is reduced by squeezing, the blood emptying itself out of the gland in a somewhat spongelike fashion. Deep palpation, especially when the neck is in extension, elicits tenderness. There is often an expansile pulsation. A thrill is felt by the palpating hand over the gland, and a bruit, systolic in time, sometimes also diastolic, rather harsh and loud, is usually heard over the gland. These phenomena, that is, the throbbing, compressibility, tenderness, thrill and bruit, are pathognomonic of a typically hyperplastic thyroid.

However, though hyperplasia is the usual pathological picture of the thyroid in Graves' disease, there are exceptions to the rule. Marine and Graham state that among the cases of exophthalmic goiter in which autopsy was performed by Crile and his associates, there were seen no normal thyroids; hyperplasia was present in about 70 percent., most of the remaining 30 percent. being adenomas, with a few colloid goiters. In my observations hyperplasia is always present, whether it be within a recently normal gland, or within an organ possessing adenomatous and colloid changes as well.

The anatomic changes of true exophthalmic goiter may lead from an active thyroid hyperplasia to a degree of degeneration, with hyposecretion. The latter explains the not infrequently occurring manifestations of hypothyroidism coexisting with or following Graves' disease as a sequel. Degenerative changes may occur rapidly or slowly, with lessening or remission of symptoms, and may result in an apparent cure of the patient.

Marine, in a review of the physio-pathology of exophthalmic goiter,

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makes the following valuable comment: "Active hyperplasia of some degree is present in probably 70 to 75 percent. of the cases routinely operated on in a large clinic. Mild degrees of fibrosis and atrophy supervening in the active hyperplasias are often seen in the late stages of the syndrome. . . . Colloid goiters (involutions from hyperplasias) are often present. Adenomas of widely different morphology have long been associated with the syndrome, and finally, there are cases of carcinoma of the thyroid with the syndrome more or less complete. . . ." Graves' syndrome associated with a carcinomatous thyroid is always secondary, consequent upon a primary malignancy of the organ.

Generally speaking, a specimen from a case of Graves' disease presents an equal enlargement of all its parts. The surface is usually smooth, but a cut section presents quite a characteristic appearance. There is seen a homogeneous structure not observable in ordinary parenchymatous goiter, with little or no visible colloid. The blood vessels are increased in size and number.

Greenfield was probably the first to show that the thyroid in exophthalmic goiter presents an increase in secreting tissue with a change of parenchyma cells from the cuboidal to the columnar shape occurring simultaneously with a diminution in the size of the acini and the quantity of colloid.

Microscopically, a hyperplastic goiter presents a reduction in the quantity of colloid; or the colloid may be entirely absent. The infolding and crowding of the cells upon the acinar spaces, the increase in the number and size of the cells, the increase in the number of alveoli, the diminution in alveolar colloid and its contained iodin,—these characteristics serve to distinguish the thyroid of exophthalmic goiter from the thyroid of simple or nontoxic goiter. Goetsch, Cowdry and others have described an increased number of mitochondria in the cytoplasm of the functioning cells of these thyroids. Mitochondria are granular, longitudinal bodies taking a characteristic stain. According to Rautmann, in Graves' disease the thyroid gland seems to have reverted to an infantile type, the histologic findings resembling those of a child's thyroid. The vesicles are little, if at all, distended, and the epithelial elements have undergone a varying degree of proliferation depending upon the degree of hyperplasia of the gland, but not necessarily upon the severity of the symptoms presented. The specimen presents a picture of glandular hyperactivity, excepting that the products of secretion are diminished or absent, having passed into the circulation almost as soon as manufactured. In early or in atypical cases, these changes may be focally or partially present; it is only in well advanced instances of the disease that the entire gland is involved in the hyperplastic changes.

Wilson, in a recent article, points out that the pathological changes in true exophthalmic goiter may be divided into three stages: 1. Early exophthalmic goiter in which there is moderate thyroid enlarge-

ment. The parenchymal cells show marked hypertrophy and moderate hyperplasia. There is diffuse hyperemia throughout the gland. 2. Advanced exophthalmic goiter in which there is advanced parenchymal cell hypertrophy and hyperplasia. There is little if any stored colloid. There is diffuse hyperemia throughout the gland. 3. Late exophthalmic goiter in which pathologically the changes in the gland are similar to those in the early stages of exophthalmic goiter but with beginning or well-marked storage of colloid. Many follicles containing colloid are lined with flattened parenchymal cells. In some instances newly developed follicles are numerous. Hyperemia is usually materially less than in glands in the previous groups. Wilson points out that the parenchymal changes in the thyroid in true exophthalmic goiter are almost always diffuse and, therefore, the gland is rarely nodular in its gross appearance.

Many varieties of atypical specimens are encountered. For example, an exophthalmic goiter, especially one of unusual size, may present one or more cysts or may present adenomatous characteristics in a portion of the gland. Rarely an exophthalmic goiter may develop secondary changes such as fibrosis. Carcinomatous changes are almost never observed in a truly hyperplastic thyroid.

5. MISCELLANEOUS PATHOLOGICAL FINDINGS IN EXOPHTHALMIC GOITER

The Thymus.—This organ is enlarged in a considerable percentage of cases. Marine and Lenhart state that the degree of hyperplasia varies with the age of the patient, the duration and severity of the symptoms, the state of the patient's nutrition, and other unknown factors. Kocher states that in nearly 50 percent. of cases of Basedow's disease there is a tendency to tardy hyperplasia or tardy evolution of the thymus. Halsted believes that the thymus in Graves' disease undergoes renewed activity. Fahr, in his series of 24 cases, found status thyomolymphaticus or persistent thymus in a few. Capelle, cited by Halsted, states that a persistent hyperplastic thymus has been found in 95 percent. of fatal cases of Graves' disease.

Blackford, in a study of 74 autopsies, found that in all subjects under 40 years there were persistent thymuses of varying size. One-half of those over 40 had a large thymus and one-half no thymus at all. From these facts Blackford formulates the following deductions: (1) The thymus plays no causative rôle in exophthalmic goiter since older people who died of that disease had no thymus; (2) the thymus may exert a protective influence in exophthalmic goiter. An apparent contradiction is evident in the two cases reported by Goodpasture, in which though the disease was of typical and progressive type, there was a mere fragment of thymus present in each instance.

Parathyroids.—Hector Mackenzie asserts that some of the more

serious symptoms of Graves' disease are due to atrophy of the parathyroid glands. Rautman claims that the parathyroids are in a state of hypertrophy or hyperplasia. Other observers also present conflicting views.

The Pituitary Gland.—Though we occasionally find cases of Graves' disease associated with evidences of acromegaly and instances in which the pituitary is affected with a growth or is hyperplastic, the majority of reports indicate that this organ as a rule does not present material pathological changes in the affection. However, some observers find changes which appear to characterize Graves' disease. Friedman, for instance, discovers chromophilia of the anterior lobe. There is also an increase in the number of basophils in this portion of the pituitary.

The Adrenals.—Observations on the pathology of the suprarenals are not numerous. Rautman has found a degree of atrophy in his cases. Pettavel, Wiesel, and Hedinger (quoted by Roussy), in cases associated with the status lymphaticus, have observed a diminution in the medullary substance of the suprarenal glands in Graves' disease.

The Pancreas.—It has been mentioned that the pancreas is depressed in function by thyroid hyperactivity, and that glycosuria and hyperglycemia are common occurrences. In view of this fact, examination by many observers yields evidences of degeneration of the islands of Langerhans, but unless there is a complicating diabetes mellitus the typical picture presented by the pancreas of diabetes is absent. Holst observed at autopsy 4 cases of exophthalmic goiter combined with glycosuria; in all of these there was found degeneration in a number of islands of Langerhans, as well as other typical changes characterizing diabetes.

Spleen and Lymphatics.—A study of the spleen has not been seriously attempted in the pathology of Graves' disease. Some observers have reported a moderate splenic hyperplasia. The *lymphatic glands* are often found enlarged. This occurs with almost the same constancy as enlarged thymus. The lymphatic tissues, especially of the thyroid, parathyroids, liver, kidneys, bone marrow and intestines, are most apt to be involved. Enlarged *tonsils* and *adenoids* often coexist, either coincidental with or as an etiological factor of Graves' disease. It seems reasonable to assume that the hyperplasia of the lymphatic tissues of the body, including the spleen and thymus, is due to the attempt on the part of Nature to protect the individual against the toxins causing the syndrome of Graves' disease.

The Heart and Blood Vessels.—Cardiac hypertrophy, dilatation or both are quite common in Graves' disease, the degree depending upon the severity and duration of the disease and the previous condition of the organ. Microscopically, we find evidences of myocardial degeneration. Fahr discovers chronic interstitial inflammation in the myocar-

dium, with collections of round cells, chiefly lymphocytes, among the muscle fibers and in the neighborhood of the blood vessels. In the large myocarditic areas the muscle fibers are separated from one another and show various degenerative changes, *i.e.*, fragmentation, dissolution, and the like. Scattered among the lymphocytes in these areas are a number of fibroblasts, while in the smaller areas there are lymphocytes only. Fatty degeneration of muscle fibers is observable only to a limited extent. Upon the basis of this evidence, Fahr believes that the toxin circulating in the body of a goiter patient may cause not only an excessive stimulation of the cardiac nerves, but further have a direct effect upon the heart muscle itself. Hashimoto, experimenting on albino rats in which he produced hyperthyroidism, was able to confirm the findings described by Fahr. Goodpasture, in a study of hearts from cases of hyperthyroidism in which death was caused by myocardial exhaustion, found acute necrosis of cardiac muscle, in one instance so diffuse as to involve a large part of the left ventricular wall. The character of necrosis was that usually associated with extreme intoxication by acute infections such as diphtheria or scarlet fever, and more commonly occurring in youth. There was no indication of an infection of sufficient virulence to be alone responsible for the necrosis. Subsequently this observer made a study to determine, first, what demonstrable effect from feeding desiccated thyroid gland, or intravenous administration of crystalline thyroxin would be produced in the myocardium; second, whether the effect of these substances would cause the heart to be more readily injured by toxic agents, notably chloroform. Animals under such treatment showed characteristic clinical symptoms with definite, although relatively slight, myocardial lesions. Similarly treated animals which had in addition been subjected to chloroform anesthesia showed more striking, widespread myocardial necrosis. These experiments indicate that chloroform as an anesthetic in cases of hyperthyroidism is apt to be exceptionally detrimental to the myocardium and should be avoided.

The Nervous System.—Wilson finds hemorrhages and areas of softening in the brain and medulla, and occasionally atrophy and sclerosis of the restiform bodies. The cervical sympathetic presents hyperchromatization, chromatolysis, atrophy, and granular degeneration of the nerve cells and nerve fibers. MacCallum does not find changes sufficiently marked to be considered important. Troussseau discovered a sclerosis of the inferior cervical ganglion with atrophy of the nervous elements. Geigel found both cervical sympathetics in the process of atrophy in a sheath of cellulo-adipose tissue. MacDonald and Moore have cited a case of fatty infiltration of the inferior cervical ganglion (Roussy).

Though occasionally slight pathologic changes are observed in the nervous system, these are not characteristic, and in the great majority

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of cases the brain, spinal cord and sympathetic system present no definite alterations.

Eyes and Orbita.—Since it is observed that the exophthalmos usually disappears after death, the theories offered to explain this sign are of but relative value. Mackinnon who performed an autopsy on an individual who died of pneumonia, in whom there was an exophthalmos of long standing originally due to exophthalmic goiter, found the retroorbital spaces filled with fat.

Other Pathological Findings.—Schioetz reports a case of exophthalmic goiter in a patient who died after rapid loss of weight, vomiting, jaundice and albuminuria. Autopsy revealed a hyperplastic thyroid, thymus, and anterior lobe of pituitary; ovaries and pancreas were atrophic, liver and kidneys degenerated. Kerr and Rusk report a case of acute yellow atrophy of the liver associated with Graves' disease. Hyperplasia of the salivary glands, incident to hyperthyroidism with or without exophthalmic goiter, has been reported by many observers. Hammerli states that a heavy thyroid is always accompanied by large salivary glands, and *vice versa*. The liver, stomach, intestines, respiratory, cutaneous and genitourinary systems present atypical evidences of thyroid stimulation which, though interesting, are pathologically unimportant.

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CHAPTER V

ENDEMIC SIMPLE GOITER

THE question of endemic goiter, or that form of thyroid enlargement dependent upon geographical causes, has been the object of attention from time immemorial. The ancient Hindus, 2000 B.C., mention treatment for goiter. Cæsar observes the frequent occurrence of big neck as characteristic of the Gauls. In fact, the term cretin originates with the Romans, who called the myxedematous idiots Christians. In 1493, Paracelsus of Switzerland first stressed the relationship between goiter and cretinism. Since then many others have written lucidly on the subject, until to-day there is an immense literature that the student of goiter might peruse.

Distribution.—Switzerland, France, Italy, Germany, India, China, South America, the United States, and Canada, all present goiter regions. The Alps, Pyrenees, Himalayas, Carpathians, and in our own country, the region of the Great Lakes, the valley of the St. Lawrence both on its American and Canadian side, and some of our Western states are inhabited by thousands of persons suffering with varying degrees of goiter. Barton's monograph on goiter among the American Indians along the shores of Lakes Ontario and Erie is noteworthy. The Goiter Commission of France, in 1874 stated that there were probably 500,000 goitrous persons and 120,000 cretins in that country. Kreuter examined in Munich 1,840 school girls ranging in age from 3 to 19; 59 percent., or 973, presented goiters of various sizes,—mostly diffuse and parenchymatous. McCarrison states that in some of the villages in Himalayan India there is scarcely a man, woman, or child who is not suffering from goiter. Waller calls attention to the Pemberton Meadows, a valley in British Columbia, a section sparsely populated by white people of various nationalities, where nearly every one is affected in greater or lesser degree with goiter. Nearly all young animals born in the district are (or were) born with goiter. Pregnant cows imported into the district have, after six months, produced goitrous calves. Such calves are very weak at birth and many die. In some cases the goiter of the calf is so large as to prove an obstruction to birth, and the cow has died. The same is true of all other domestic animals. About 80 percent. of foals die, owing to weakness at birth. With pigs, most of the litters come hairless, either dead or too weak to survive. Chickens are weak, find difficulty in chipping the egg, and great numbers die.

Even pigs imported with their mothers are very likely to show snuffles (rickets or cretinism) which keeps them forever stunted, crippled and distorted. Grown pigs often break down in the pastures from softness of the bones. Fowls sometimes die with huge goiters, possibly from suffocation by pressure on the windpipe, and cocks often lose their power of crowing from the same cause. Many of them suffer from goiter, and some are devoid of feathers. With regard to children, babies born in the district are usually goitrous, though not apparently weak like the young animals. If fed on imported condensed milk and only water that has been boiled, infants can be kept free from goiter, but those fed on milk produced in the district soon become infected.



FIG. 28.—Large goiter from endemic region in France.



FIG. 29.—Peculiar double goiter from endemic region in Italy.

In South America, Monge observes that there are unusually large-sized goiters encountered in the Urubamba district of Peru. About 2 percent. of the inhabitants were cretins in certain districts, and a cretinoid condition was still more common. Goiter is endemic especially in the Andes region and certain mountainous territory in the tropics. In Brazil it was thought that endemic goiter was caused by *Trypanosoma cruzi*, discovered by Chagas. Kraus and his co-workers pointed out that in Argentina goiter was found in places where *Triatoma infestans*, the insect carrier of *Trypanosoma*, prevailed. Recently, however, Houssay has succeeded in producing experimental goiter in white rats after feeding them with water from the province of Salta. He believes that these investigations should be repeated on a large scale on account of their great theoretical and practical importance, and confirms the theory that water is one of the transmitting agencies of goiter.

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Mayo observes that there is a tremendous amount of goiter in this country. Comparatively few of the cases occur in New England or in the Southern States. There were about 3 cases of goiter to each 1000 of draft recruits in the district of New York, 7 cases to 1000 in the Great Lakes region, 8 or 9 cases to 1000 in Montana, and 14 cases to 1000 in Oregon, Washington, and Idaho. In a discussion following a paper by Crile in 1919, it was brought out that there are 15 goiters per 1000 men in the northern Pacific states, and that there is almost no goiter in New Hampshire and Vermont. W. J. Kerr, in a survey of 21,182 recruits from eleven Northwestern states, found simple goiter to be highest in Washington and Oregon and lowest in California and Nevada. Twenty-one percent. of all troops showed definite enlargement of the thyroid gland, of which 27 percent. were rather large. Goiters had been noticed in other members of the family, especially the females. Levin examined 1,783 individuals in Houghton County, an area in the Lake Superior region of Michigan, their ages ranging from newborn to 61 years. One thousand one hundred and forty-six had enlarged thyroids with 682 simple goiters, 420 adenomas and cystomas, and 44 colloid goiters. Tolman claims that volcanic formations, the Crystalline rocks of the Archaic period, and all deposits laid down in fresh water are free from goiter-producing characteristics. In the United States the greatest endemicity is found in Paleozoic areas. Tolman estimates the number of goiter cases in West Virginia as 12,000. Brendel, in an examination of 8,951 drafted men, showed that goiter is more common in young men from the Northwestern states than the experience of the general practitioner would suggest. Apparently there are definite goiter districts existing in Oregon, Montana and probably in Nevada. Locality seems to be of greater etiological importance than heredity. Among 26,215 pupils examined in the schools of Grand Rapids, Mich., by Reed and Clay, 30 percent. had enlarged thyroids; of these, 32 percent. were boys and 67 percent. girls. Middleton remarks that in the Virgin Valley of southern Utah 75 percent. of women have some form of thyroid enlargement; in the Salt Lake Valley, on the other hand, due to proximity to saline waters, goiter is a relatively uncommon condition.

McClendon and Williams report the result of an analysis of the iodin of water in various "zones" of the United States in its relation to the number of goiters found in drafted men, the total number of men examined being 2,500,000. In the zones in which the greatest number of endemic goiter is found (15.30 goiters per 1000 men), corresponding to the Northwest and about the Great Lakes, the iodin in parts per billion of water is 0.01 to 0.1; in the next most important zone corresponding to states bordering upon the first zone (5.15 goiters per 1000 men), the iodin in the water is 0.015 to 1.2; in the third zone, extending farther off, stretching across the country (1.5 goiters per 1000 men), the iodin content of the water is 0.06 to 9; and the fourth zone, including the South-

ern States and the fringe of states nearest the Atlantic Ocean (0.1 goiters per 1,000 men), the iodin content is 1.4 to 10 per billion parts of water. W. P. Kerr in an examination of 310 Indian students representing 43 tribes from six states and Alaska found that 10.6 percent showed definite enlargement of the thyroid. The survey shows that in all full-blooded Indians the incidence of goiter is very low as compared with part blood or the pure Caucasian race.



FIG. 30.—Comparison of iodin in water supplies and distribution of goiter: iodin in parts per billion of representative rivers; goiter rate per thousand. Defects Found in Drafted Men, War Department, 1920; curves smoothed.—(Kind permission of Dr. J. F. McClendon and Editor of the *Jour. Am. Med. Assn.*)

Heredity.—Porter and Vonderlehr report 4 cases of congenital goiter in boys, aged 3½, 6, 8, and 14 years, occurring in the southwestern part of Virginia, where goiter is endemic. None of the boys presented any symptoms of either hypo- or hyperthyroidism, any mental aberration or abnormal development. The consistency of the enlargement was soft, but suggestive of the colloid type. *Ascaris lumbricoides* was found in the stools of all the children. Schlesinger observes that hyperplasia of the parenchyma of the thyroid in countries with goiter may begin with newborn infants. It begins most frequently at the age of 6 in girls or 9 in boys. Hamburger, in speaking of goiter in infants in Steiermark, states that when children with stridor show an increase in the symptoms when the head is bent backward, there is probably a

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substantial goiter. De Quervain, in a paper read at the meeting of the Swiss goiter commission, agrees with Hunziker that goiter represents the way in which the thyroid adapts itself to an inadequate supply of iodin in the food. But he urges that as the thyroid is found abnormally large in all the infant cadavers in the Swiss goiter centers, and as he found that fully 75 percent. of all the children entering school for the first time at Bern have appreciably enlarged thyroids, prophylaxis must begin before the school age. To be effectual, it must be begun with the mother, and this is practicable only with iodized salt. The aim must be to prevent goiter in the rising generation. Schlesinger observes that in regions where goiter is endemic, the newborn often show transient hyperplasia of the thyroid, but it subsides in a few months. A second wave sets in at the age of 6 to 7 in girls, 9 in boys, and reaches its height before or during puberty.

Specific Etiology.—With respect to the causation of goiter, McCarrison thus sums up the question: "The problem of the causation of goiter is one which has exercised the minds of observers since the earliest days of medical history. There are, indeed, few diseases about which so much has been written and so many diverse views propounded. The association of goiter with mountains has led to the promulgation of many of these views. A causal influence has been attributed to the configuration of the soil, to waters derived from certain soils and charged with chemical ingredients, to altitude, to the rarity of the atmosphere, to cold and dry air, to air holding too little oxygen and to air holding too much, to air laden with sulphurous vapors, to the action of cold air on the neck, to a want of iodin in the air, to air charged with electricity, and to some half hundred other such causes. One is apt to dismiss with scant ceremony the observations of earlier observers in this field of research, but if we consider some of their views in the light of our modern knowledge of the thyroid function, we shall realize the truth that is in many of them. The effect of altitude and of rarified atmosphere falls into place with the gland's function of regulating the respiratory changes and of maintaining the red blood corpuscles and the hemoglobin at a level proper to the altitude. The lack of iodin in the air at altitudes of about 1000 feet will indirectly influence the thyroid toward hyperplasia by its lack in the food. The ingestion of waters charged with an excess of lime adds to the burden of the thyroid's numerous duties. Even configuration of the soil by favoring the entry of surface drainage into unprotected water supplies, is not without considerable influence in the genesis of the disease."

McCarrison, after a large amount of experimentation and epidemiologic research, presents the following facts:

- (1) In goitrous villages situated one above the other on an unprotected water supply, the incidence of goiter steadily increases

from above downward, depending upon the increased impurity of the water.

- (2) Goiter has been produced in the human subject by the ingestion of the residue left on the candle of a Berkfeld filter after infiltration of goitrogenous water. This residue when boiled does not cause the disease.
- (3) The administration of intestinal antiseptics, *e.g.*, betanaphthol or thymol, causes the disappearance of recent goiters in young subjects. Lactic acid bacilli administered daily to recent cases of goiter may cause the complete disappearance of the swelling.
- (4) The cure of chronic constipation and intestinal stasis associated with goiter, as by the operation of short circuiting or colectomy, causes the disappearance or marked reduction in the size of the goiter (Lane). This proves intestinal toxemia as the causal agent.
- (5) Fish confined in tanks situated one above the other on a single water supply, show an increasing proportion of thyroid hyperplasias from above downward. The addition of iodin or the like has a prophylactic or a curative influence upon the hyperplasia.
- (6) The administration to rats and dogs of the scraped deposit found on the inner surface of the water-soaked wooden tanks in which the fish are confined, produces thyroid hyperplasia and goiter. This substance is rendered innocuous by boiling (Gaylord).
- (7) Rats, goats, and other animals are rendered goitrous by being fed on fecal material from goitrous and even nongoitrous subjects.
- (8) Vaccines prepared from intestinal organisms are capable of causing a disappearance of recent cases of goiter when injected in appropriate doses at weekly intervals.

McCarrison therefore concludes that the causal agents of goiter are microorganisms inhabiting the alimentary canal of sufferers from this disease, and often of other persons whose thyroids show no actual enlargement but which, nevertheless, may be in a hyperplastic state. These germs reach the alimentary tract through infected soil or water, and such an infected individual may become the "carrier" of the infecting agents.

An apparent contradiction to the water theory is seen in the results of Kappenburg's experiments on rats. He found little difference in the size of the thyroids in wild rats, whether they had lived in places with no goiter or where it is prevalent. In Utrecht, goiter is very frequently seen; in Sneek, a little town in the north of Holland, it is never observed. Rats in Sneek were given water from Utrecht to drink. No goiter resulted, nor any histological abnormalities. Similar animals kept under a comparable régime at Utrecht developed thyroids twice as large as normal; histologically they showed to greater or lesser degree the

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changes characteristic of goiter. Boiling the water did not prevent the thyroid enlargement. The author concludes that the rôle played by drinking water in the etiology of goiter is still problematic and that, in fact, it is not proved that it plays any part at all.

Hawks believes that the cause of the prevalence of goiter in the middle West is due to the drinking of the subterranean water of the glacial drift, which is analogous in its composition to the glacial waters of Switzerland, where goiter is so prevalent. Bayard compares goiter to beriberi, a deficiency disease, in that both may develop when patients go from one country to another, owing to differences of food encountered, iodin being the lacking factor in the case of goiter. Especially during youth the organism needs a large amount of iodin. The less iodin in the food the larger is the thyroid. Hawks observes that in Kiel, situated at the seaside, the average thyroid is smaller than in Berlin. In Berlin it is smaller than in Munich. The size of the gland in Bern is larger than in Munich. The greater the distance from the sea, the larger the size of the thyroid. Meisbach, too, remarks that in Bavaria goiter is probably due to the low iodin content of the water.

Artificial Goiter.—Goldemberg makes the interesting observation that the addition of 2-3 mg. sodium fluorid to the food of young white rats during a period of 6 to 8 months produced chronic intoxication with retarded growth. The thyroid increased in size, its parenchyma became compact, with considerable cellular hyperplasia. The author considers that this enlargement amounts to experimental goiter. This observer, in a later communication, expresses his belief that fluorid in the drinking water is responsible for endemic goiter.

Racial Immunity to Goiter.—The Japanese appear relatively immune to goiter. This is due to the inclusion in their diet of seaweed, which is rich in iodin. The marked influence of diet upon the size and activity of the thyroid gland has been known for some time. Races of people accustomed to a dietary deficient in iodin suffer with goiter in greater degree than those subsisting on foods rich in iodin. Food rich in animal proteids or a dietary rich in fleshy substances increases the activity of the thyroid gland with concomitant loss of stored up thyroid secretion which is thrown in excessive quantities into the blood. It is for this reason that a dietary containing a minimum of flesh, or what is best, an absence of animal foods and a maximum of vegetable products, is the ideal regimen for subjects susceptible to or suffering with goiter.

Treatment.—Unconsciously, iodin has been employed in the treatment of goiter for many centuries. In ancient Greece, sponges were burned, and the ash was administered internally to goitrous patients. Hippocrates, Galen, Pliny, and even the Chinese fifteen centuries before Christ used burnt sponge in the treatment of goiter. Passing on to Coindet, in 1820, and to 1895, the time of the discovery of iodin in the normal thyroid gland by Baumann, and to Oswald's discovery of iodo-

thyroglobulin in 1901, considerable progress was made. It was Chatin, however, in 1850, who first stated that endemic goiter probably followed the drinking of water of a low iodin content. His hypothesis was not taken seriously until years later. The most significant work in recent years was done by McCarrison, and Marine and his associates,— Kimball, Lenhart, and Rogoff. In 1921, Marine and Kimball, in discussing endemic goiter as a deficiency disease, pointed out the following facts:

1. The active principle of the thyroid is a very stable organic compound of iodin. . . .

2. The developmental stage of all goiters is characterized by an increased blood flow, an increase in the size and number of epithelial cells, a decrease in the stainable colloid, and a marked absolute decrease in the iodin store. The decrease in the iodin store precedes the cellular hypertrophy and hyperplasia.

3. Similar changes (compensatory hyperplasia) invariably occur in the remaining portion of the gland, when a sufficient portion of the entire gland is removed. The amount of gland it is necessary to remove in order to cause compensatory hyperplasia varies somewhat with the species of animal, with the age, diet, and the presence or absence of iodin.

4. The administration of exceedingly small amounts of any salt of iodin in any manner completely protects the remaining thyroid against compensatory hyperplasia, even after the removal of three fourths of the normal gland in cats, dogs, rabbits, rats and fowls. . . .

5. If most of the thyroid gland is removed before or in the early stages of pregnancy, and rigid precautions are taken to exclude iodin, the young at birth will have enlarged thyroids, as first shown by Halsted in dogs; while, if iodin is available, the young at birth will have normal thyroids.

6. A milligram of iodin, given at weekly intervals, has been found sufficient to prevent thyroid hyperplasia in pups.

7. Thyroid tissue has an extraordinary affinity for iodin, as has been demonstrated in *in vitro* perfusions of surviving thyroids, and also by injecting intravenously small amounts of some soluble salt of iodin into the intact animal.

8. If the iodin store in the thyroid is maintained above 0.1 percent., no hyperplastic changes, and therefore no goiter, can develop.

The first instance of preventing goiter on a large scale was accidental and in connection with the sheep raising industry of Michigan. Prior to the discovery of salt deposits around the Great Lakes, the future of the industry seemed hopeless; but with the development of the salt industry and its use by the sheep growers, goiter rapidly decreased. The explanation, as furnished by Marine, is that salt contains appreciable quantities of both bromine and iodin. The second

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instance of goiter prevention on a large scale was in brook trout, and the disease was averted in the hatcheries by the use of tincture of iodin added to the water in concentration not exceeding 1 to 1,000,000.

In a census taken by Marine and Kimball of the condition of the thyroid in the girls from the fifth to the twelfth grades of the school population of a large community in the Great Lakes goitrous district, it was found that 1,688, or 43.59 percent. had normal thyroids; 2,184, or 56.41 percent., had enlarged thyroids; and 594, or 13.4 percent., had well-defined, persistent thyroglossal stalks. In a report published in 1920, these observers found that in the three communities of Akron, Cleveland, and Warren, Ohio, the percentage of relation of school children with normal and enlarged thyroids was as follows: (1) *Girls:* 9,679 (examinations extending through 3 years) were examined in Akron—51.36 percent. had normal thyroids and 48.64 percent. had enlarged thyroids; 406 were examined in Cleveland—62.31 percent. had normal thyroids and 37.69 percent. had enlarged thyroids; 925 were examined in Warren—75.57 percent. had normal thyroids and 24.43 percent. had enlarged thyroids. (2) *Boys:* 273 were examined in Cleveland—81.68 percent. had normal thyroids and 18.32 per cent. had enlarged thyroids; 911 were examined in Warren—90.45 percent. had normal thyroids, 9.55 percent. had enlarged thyroids.

For the prophylactic treatment Marine and Kimball selected sodium iodid on the grounds of economy and ease of administration. In all their dispensary experiments with children, the author used either syrup of hydriodic acid or syrup of ferrous iodid, in 1 c.c. doses daily for two or three weeks, repeated twice yearly. They arbitrarily selected to use 2 gm. sodium iodid, given in 0.2 gm. doses each school day, for each pupil in the fifth, sixth, seventh and eighth grades; and 4 gm. given in 0.4 gm. doses each school day for each pupil in the ninth, tenth, eleventh and twelfth grades. This was given twice annually about the first of May and December, at the schools, by the teachers or nurses. The summarized results of a reexamination by these observers, made 6 months later, of all girls from the fifth to the twelfth grades, show that not a single pupil in whom the thyroid was normal at first and who was given iodin showed any enlargement, while of those not taking iodin 26 percent. showed definitely enlarged thyroids, and some moderately large goiters. The treatment, in addition, proved of curative value; one-third of the goiters marked "small goiters" disappeared; and one-third of these marked "moderate goiters" showed a decrease of 2 cm. or more.

Commenting upon these facts, an editorial in the *Journal of the American Medical Association* (October 21, 1921), remarks that the value of iodin in the simple thyroid enlargement in the fetal period, in pregnancy, and in animal nutrition in general cannot be overestimated. "What it means in animal nutrition and how easily danger can be

averted has largely been emphasized in the studies of fetal athyreosis and the hairless pig malady of some of the Western states."

Marine and Kimball conclude that the maximum of prevention of endemic goiter coupled with the minimum of effort, would be obtained by giving iodid between the ages of 11 and 17 years. The iodid rash prophesied by some critics failed to materialize in any noticeable way in more than 5 girls, in whom it was transitory and uneventful, promptly clearing up when the treatment was stopped.

These investigators also give assurance that there is no danger of producing a toxic condition like exophthalmic goiter under this prophylactic régime, as not a single symptom of this alleged danger from the use of iodid was encountered. Nor was anything different to be expected; for, as Marine and Kimball remind us, the risk of inducing manifestations of exophthalmic goiter from the use of iodin in physiologic doses is exceedingly small, even in those cases in which there were large hyperplastic thyroids, that is, the kind of thyroid enlargement that would permit of the most rapid formation and excretion of the iodin-containing hormone. However, Bircher, Baumann, Chapman, Oswald and others have sounded a warning against over-enthusiasm in the use of iodin, which may lead to its abuse with considerable, and occasionally irreparable harm.

Hunziker, in his studies on the prevalence of goiter in Switzerland, was able to confirm the studies of Marine and his associates. He suggests that iodin-containing manure in the regions where goiter is endemic might supply the vegetables with the needed iodin, and thus exterminate goiter. A year of such "fertilizing" of human beings with salt made with an admixture of iodin would go far toward solving the problem. Hunziker and Wyss, in a report based on observations on a group of 775 goitrous school children, administered approximately 1 mgm. of potassium iodid per week throughout the year. This procedure was found both to reduce goiters already existing and to prevent goiter formation in the normal individual.

Hotz of Switzerland points out that thyroid prophylaxis for children is a pressing necessity in his country and should be carried out on an extensive scale with governmental assistance. Iodin, though generally useful in prophylaxis and treatment, should not be administered to older women, especially the hard working class in whom goiters are very prevalent and associated with premature age. In such types the iodides may result in a depletion of body strength and the production of an artificial Basedow's disease. Klinger reports the results of the administration of small doses of iodin on the prevention of simple or endemic goiter in children in 7 Swiss schools in the region around Zurich. His observations cover a period of 15 months. He used both sodium iodid and a proprietary organic preparation, "Iodostarin," preferring the latter because it is more palatable. He began the treatment with 30 mgm.

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(approximately $\frac{1}{2}$ gr.) iodid at weekly intervals, and after 3 months reduced the dose to 10 mgm. weekly. Before beginning the prophylactic treatment he conducted a careful survey of the incidence of goiter among the children. In some school districts as high as 95 percent. of the children between the ages of 6 and 10 years had enlarged thyroids, and in other districts probably 82 percent. at the time of the initial survey. The age group 10 to 14 years showed a still higher incidence of goiter, even 100 percent. In over 1000 cases observed for 16 months, no untoward effects were noted from iodin administration, not even a single case of iodism. He calls attention of physicians to the fact that fear of untoward effects (iodism or iodin-Basedow) even from the use of excessive physiological amounts of iodin (3-5 mgms. weekly) are without foundation, and concludes that endemic goiter in children may be completely controlled at a nominal cost by the simple expedient of giving 3 to 5 mgm. iodin once or twice weekly over a period of a month, and repeated each Spring and Autumn.

Kjlstad states that goiter is extremely prevalent in the Telemarken district in southern Norway, southwest of Christiania. In one school at Lunde, 80 percent. of the children have goiter. Most of the goiters subside under iodin.

In an effort to provide an inexpensive routine and popular prophylactic, Sloan suggests the use of iodized table salt especially in those regions which are considered goitrous. To be efficient the concentration of the iodin does not need to be more than 1 in 5000. If salt containing this minute quantity of sodium iodid could be used for all individual household purposes throughout the goiter belts, it is Sloan's opinion that the development of endemic goiter in the second generation would be prevented and that other goitrous conditions would not be exaggerated. Weith relates that large mouthed bottles containing 20 gm. of 10 percent. tincture of iodin were placed in all the school rooms of several of the school buildings at Lausanne. Examination of the children after two months of this showed only 495 with goiter when there had been 651 to start with, and more than 50 percent. showed marked retrogression.

SUMMARY

1. Endemic goiter has been a problem for many centuries, and is widely distributed throughout the world.
2. In the North American continent, especially in the United States, the problem is vital, threatening and afflicting many thousands of inhabitants.
3. The specific etiology of endemic goiter is a geographical deficiency of iodin in the air, food, or water, resulting in an iodin content in the thyroid of the inhabitants of less than .1 percent.

4. Iodin administration is the prophylactic of endemic goiter and the cure of early cases. Kimball and his associates suggest as a public health measure the use of 2 gm. sodium iodid over a period of 2 weeks, repeated twice a year. This dosage has prevented enlargement of the thyroid in more than 99 percent. of the children in a mildly goitrous district.

5. Iodin must be given in minute doses, under careful supervision, as unnecessarily large doses may lead to serious untoward effects.

6. *Endemic simple goiter* must be discriminated from *sporadic simple goiter*, as their prophylaxis and treatment differ in many respects. This differentiation will be discussed in the next chapter.

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CHAPTER VI

SIMPLE NONSURGICAL GOITER

By simple nonsurgical goiter is here meant simple parenchymatous and colloid goiter, the two most common forms of thyroid enlargement seen in practice. Simple nonsurgical goiter may be of *endemic* etiology as described in the last chapter, or it may be due to *sporadic* causation and therefore not dependent upon geographical conditions.

SPORADIC VERSUS ENDEMIC GOITER

In contradistinction to *endemic* goiter, by which term is meant thyroid enlargement occurring constantly in certain districts, the term *sporadic* goiter indicates thyroid enlargement as a result, not of geographical conditions, but of causes known and unknown, occurring everywhere. Although the pathological and clinical pictures of the two etiologically different types of simple goiter may be identical, the one is due to deficient iodin intake, the other to complex physiological and miscellaneous causes.

In the distinction between endemic and sporadic simple goiter, we must include a consideration of susceptibility to or immunity from, as the case may be, the etiological factors in goitrous districts on the one hand, and factors, not geographical in origin, but favoring the development of goiter, on the other. It is easy enough, in a non-goitrous district, to conclude that a given goiter is sporadic in nature. It is rather difficult and often impossible, to make the distinction in patients residing in goitrous districts, as to whether the thyroid enlargement is induced by geographical conditions or otherwise.

COMPLEX ETIOLOGY OF SPORADIC SIMPLE GOITER

The reason for failure and even harm resulting from the use of iodin in the prophylaxis or treatment of non-endemic goiter is not far to seek if we but remember the known etiology of this type of thyroid enlargement. Let us recall that sporadic goiters may be due to the following factors, none of which is dependent upon a deficiency of iodin intake:

1. **Heredity** seems to play an important rôle. In my observations, this seems true in at least 40 percent. of patients. On glancing through my records at this writing, I find quite a number of instances in which

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there are three or more immediate members of a family presenting goiter.

2. Puberty, Adolescence, Pregnancy, Lactation, the **Menopause** and even the ordinary **Menstrual Function** in established adult life, are productive of thyroid swelling in susceptible individuals. I say susceptible because, aside from hereditary tendencies, it is difficult to understand why one person does and another does not, under the same circumstances, develop thyroid enlargement. There is a direct and



FIG. 31.—Goiter in mother and four daughters. An example of familial tendency.

striking relationship between the functions of the organs of reproduction and the thyroid apparatus. In this connection, we might state that

3. Diseases of the Female Reproductive Organs, eminently ovarian and uterine conditions, are often etiologically responsible for goiter formation. Disease of the female reproductive organs and the foregoing factors of puberty, adolescence, pregnancy, lactation and the menopause are responsible for the great preponderance of goiter in females. The sex incidence of goiter is variously stated by various observers. From 20 females to 1 male, the proportion is stated to be 10 to 1, 5 to 1, and even 2 to 1. In my observations, simple sporadic goiter appears in the proportion of approximately 8 females to 1 male.

4. Focal Infections from teeth, tonsils, nasal sinuses, and more remotely from the gastro-intestinal and genito-urinary tracts are commonly responsible for thyroid enlargements.

5. Acute Infectious Diseases, especially acute articular rheumatism, influenza, and typhoid fever, may instigate goiter formation during, but more often following, the course of the affection. Such chronic infections as tuberculosis and syphilis likewise play an etiological rôle.

6. Miscellaneous Causes, little known or unknown in nature, which, for want of a better heading, might be placed under that excuse for ignorance, the term "idiopathic," form another etiological group. Probably here may be included numerous instances of marked dietary indiscretion in which the thyroid gland is forced to hypertrophy in its function of detoxication.

We may safely accept the generalization that, with few exceptions, in sporadic simple goiter the etiology is one operating on a basis of excessive demands for thyroid hormone away from the thyroid; the organ, incapable of supplying this excess, must hypertrophy in efforts at physiological adjustment.

Mode of Onset of Sporadic Goiter.—The goitrous process may be acute, chronic, recurrent, or intercurrent. Rarely a compensatory hypertrophy or colloid goiter may have an acute occurrence and appear prominently within a week or two following an exciting cause of which the patient may or may not be cognizant. Thus, in a recent patient of 47 with a moderately resistant goiter as large as a medium sized lemon, involving the isthmus and right lobe of the thyroid, it was stated that the mass made its appearance a few days after the contraction of a cold. In another instance, a Civil War Veteran of 78, his daughter claims to have suddenly discovered the "large neck" while shaving the patient. Ordinarily, the onset of simple sporadic goiter is gradual, appearing often at the early age of 6 or 7, occasionally at birth, but most often a year or two prior to menstruation, increasing in size as this function is established. Often the tendency to goiter does not assert itself until menstruation is established, quite commonly during pregnancy, and least of all during the menopause.

Let us now discuss the prophylaxis of simple nonsurgical sporadic goiter.

PREVENTION OF SPORADIC SIMPLE GOITER

In the prevention of sporadic simple goiter the hereditary tendency is a strong factor to be taken into account, and prophylaxis must begin before birth of the individual. The pregnant mother who is susceptible to or already has a goiter must be under careful supervision with regard to the necessary equilibrium of the endocrine functions. This is accomplished through ample physical and mental rest, the proper dietary and personal hygiene, and the guarded administration of thyroid extract. Incidentally, thyroid opotherapy will reduce to a minimum the possibility of eclampsia.



FIG. 32.—Goiter in Civil War veteran of 78, who claims that it developed over night, his daughter having suddenly discovered it while shaving him.

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In instances of strong hereditary tendency, ideal prophylaxis must be instituted at the birth of the individual. The child born of goitrous parents will not necessarily become goitrous, though without medical supervision over a period of years, the chances to become afflicted with goiter are great. During infancy, the hygiene, diet, and occasional medication are the principles of prophylaxis. In addition, the growing child should be guarded against excessive physical and mental stress and strain incident to school life. Puberty and the onset of the menstrual function constitute a prolonged period of anxiety and peril. At this time too much care cannot be given the individual with goitrous parents, for if thyroid enlargement has been avoided heretofore, the crucial test is reached, and the organ may become swollen as an incident to the first menstruation, with permanent goiter formation. The girl must have explained to her the nature of the menstrual phenomenon, and she must be instructed in its hygiene. All physical and mental duties must be curtailed or discontinued, and the subject should stay in bed during the active period of menstruation. *This precaution taken monthly will do more than anything else in the prevention of sporadic simple goiter. To state it more plainly, the continuation of the usual mental and physical duties during menstruation in young girls is productive of the great majority of sporadic simple goiters seen in our midst.*

The marital relations, pregnancy, lactation, and the menopause, occurring in persons with an inherited tendency toward goiter, likewise require guidance of the medical attendant, with or without thyroid ophotherapy.

With regard to the prophylaxis of simple sporadic goiter resulting from the infections, little if anything can be said. Usually the patient presents herself for the treatment of an already well developed thyroid enlargement of varying duration; sometimes the goiter has existed for years, and the medical attendant, searching for etiological factors, discovers it to be of infectious origin either in the nature of a previous attack of acute infectious disease, or in a coexisting pyorrhea, tonsillitis, sinusitis, salpingitis, appendicitis, and the like. Rarely, if ever, are we called upon to prevent goiter originating from a focal infection; it is its cure that claims our attention. However, in each patient a painstaking history and physical examination must be made for the purpose of discovering tangible causes of goiter. Infected tonsils or sinuses, decayed teeth, pyorrhea alveolaris, constipation, infected gall bladder or appendix, pelvic infections or neoplasms,—all these must be borne in mind, sought for, and, if discovered, eliminated. Nevertheless, while the causes just mentioned have been proved excitants of goiter formation, their removal in a given case does not always cure the goiter. In a certain percentage of instances in which a tonsillectomy is indicated and performed, the thyroid gland will subsequently undergo involution

and become normal in size again. In the majority of cases, however, an infectious focus having been partially or wholly responsible for the existence of goiter, the latter will be uninfluenced in its course by the removal of the former. Indeed, I have seen a few instances in which the very removal of infected tonsils in a patient with thyroid hypertrophy was followed shortly thereafter by a still further increase in the size of the goiter. This, of course, is an exception to the rule, but such instances occur. Occasions of this sort must not deter us, however, from doing our duty in a scientific way, for infectious foci and other discoverable causes require our attention in all cases.

DIET IN SIMPLE NONSURGICAL GOITER

The qualitative aspect of the diet is too often ignored in the management of these patients. It has been amply proved experimentally and clinically that flesh foods favor proliferation of thyroid tissues, *i.e.*, goiter formation. The same may be said of all other substances possessing somewhat toxic properties, such as tea, coffee, alcoholic substances, the spices, condiments, and the like. It is surprising to note how many of these patients are very fond of tea and coffee, sour pickles, and plenty of meat. These errors must be corrected. Orders must be given with *precision*. Merely to *tell* the patient to restrict this, eliminate that, and be careful not to exceed another article of food or beverage is to court failure in treatment. The patient must be made to understand that unless orders are obeyed religiously, further growth and certain changes will occur in the goiter, and the knife will be required. It must be insisted upon that team work,—sincere efforts of both patient and doctor are necessary to achieve the required results in a minimum of time. Patients who are uncertain and vacillate in coöperation had better be refused treatment.

It is always best to give the patient a diet list. The following is a specimen menu which I am giving these patients:

DIET LIST AND MENU SUGGESTIONS

GENERAL REMARK: TAKE A MINIMUM OF FLESH FOOD, OR PREFERABLY, NO FLESH FOOD AT ALL.

Breakfast

Fruit: Orange, grapefruit, stewed prunes, over-ripe bananas and cream, baked apple and cream, cantaloup, honeydew.

Cereal: Oatmeal, barley, rice, farina, "grape nuts," buckwheat cakes, hominy, mush.

Eggs: Soft boiled, poached, fried, scrambled, as desired. (Use no lard.)

Bread and Butter or Buttered Toast: As much as can be eaten.

Beverage: Milk (hot or cold). "Postum," chickory infusion, or hot chocolate.

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Luncheon

Cheese (fresh cream or cottage) with brown sugar and cream.
Potatoes (baked, mashed, boiled, French fried without lard), or potato fritters.
Legumes: Small quantity peas, beans, lentils.
Green Vegetables: Cauliflower, spinach, lettuce, red tomatoes, squash, cucumbers, asparagus, carrots, onions, beets, corn on cob, egg plant, oyster plant.
Plenty of bread and butter or jam (made of figs, cherries, plums, blackberries).
Stewed fruit: Apples, peaches, pears, raisins, prunes, cherries, apricots.
Beverages: As at breakfast time.

Dinner

Soup: Vegetable, barley, rice, noodle, potato, corn (not canned), onion, bean.
Meat: One lamb or veal chop, or small portion of fowl or fish.
Fritters: Apple, banana, peach, corn, potato, squash.
Dessert: Puddings made of bread, apples, rice, tapioca, cornstarch, chocolate, raisins, nuts, figs, dates; cup custards; small quantity of bitter sweet chocolates, chocolate peppermints, chocolate coated nuts.
Beverage: As at breakfast time.
(REMARK): Butter, Crisco, and olive oil are the only fats permitted.
Candy is never to be eaten between meals. Additional beverages such as buttermilk, kephyr, sour milk, and water may be taken throughout the day.

The Following Substances are Strictly Forbidden:

All kinds of delicatessen and canned goods, spiced cheeses, hot breads, pastries and the like, under-ripe bananas and under-ripe fruits of all sorts, strawberries, watermelon, blackberries, huckleberries, gooseberries and raspberries.
Condiments of all sorts, especially pepper, horse radish, mustard, catsup, vinegar, sour pickles or tomatoes, and the like.
Beverages: Tea, coffee, cocoa, lemonade, alcoholic substances, an *excess* of carbonated beverages.
REMARKS: Avoid the extremes of temperature in food or drink. Eat slowly and chew your food thoroughly.

In giving the patient dietary instructions, it is well to make somewhat of the following explanation with regard to the marked reduction or omission of flesh foods: "Meat contains both food and poison; you cannot separate the two; you take both when you eat meat. An important duty of the thyroid gland, from which goiter springs, is to protect the body against poisons. Persons without goiter can cope with these poisons fairly satisfactorily. You have goiter, which indicates that your thyroid is already too busy with poisonous products successfully to combat poisons in food. The continuance in your diet of meat and other things which you have been forbidden, would mean a further enlargement of the neck. Hence you must be careful about what you eat and consult the diet list often."

Qualitative Variations in Diet.—A percentage of these patients present evidences of hypothyroidism associated with excessive weight.

In some it may be necessary to reduce the quantity of food in varying degree. Most often, thyroid ootherapy, to be discussed under medicinal treatment, is sufficient to bring the weight to a more normal figure. In extreme obesity, it is probably advisable to suggest the omission of one meal a day, breakfast for instance, and further to suggest a reduction in the quantity of the two remaining meals. Qualitative adjustment of the diet in accordance with the principles of dietetics in obesity and also the matter of fluid intake, may be considered in extreme cases.

In the average patient with early simple goiter, the weight is approximately normal, and no orders are required with relation to the quantity of food intake. It is the qualitative aspect of the diet only, as emphasized by the diet list, with which we are concerned.

However, if we must employ thyroid ootherapy, I am in the habit of urging the patient to retain a 10 pound increase over and above the normal standard of weight for the individual if an adult, and an increase less in proportion if a child. The reason for this is that thyroid ootherapy, our medicinal mainstay, may tend to diminish weight, and the proper quantity of food would prevent loss in weight and assure a safeguarding gain, depending upon how much the food is increased.

Patients who are undernourished must indeed be instructed in forced feeding and may be given a diet list similar to the one which will be found in the chapter on Diet in Exophthalmic Goiter. This list contains ample directions, which, if followed, will certainly bring the weight up to almost any desirable figure. In those patients with simple goiter who are at the same time underweight, the forced feeding question is very important for two reasons: (1) Because in the treatment of morbid conditions we can best accomplish our purpose with a normal weight, which is most often an index of satisfactory reparative or recuperative processes to assist our therapeutic efforts; and (2) because the medicinal treatment directed toward the reduction in size of the thyroid may tend further to decrease the weight unless we order a diet to offset this. Hence, the diet has for its purpose both an increase in the bodily vitality and weight to the normal and the control of the reducing tendency on the part of medication given the patient. Many difficulties may be encountered with these undernourished patients when the matter of forced feeding is urged upon them. The main obstacles are first, the fact that these individuals are usually attending school, or at work, or otherwise performing daily duties during which they are not in position to take more than the habitual quantity of food, and second, the so-called small capacity habit of the stomach. This habit of taking a quantity of food below normal, which may have characterized the individual for years, must give way to the habit of taking a normal, later a slightly excessive quantity, depending upon individual needs. The task offers difficulties, but by proper conviction and persuasion the medical attendant usually succeeds in his efforts to secure the necessary team work.

THE MEDICINAL TREATMENT OF SIMPLE NONSURGICAL GOITER

While a percentage of patients suffering with simple parenchymatous and colloid goiter recover without medication on the disappearance of the cause, it is unsafe to depend upon spontaneous recovery. It would be taking a chance with the patient; thyroid involution may not occur—Nature may err. Indeed, the goiter may continue to increase in size, undergo changes, and become less amenable and frequently not at all amenable to nonsurgical efforts at cure. It is for this reason that the physician should step in and direct Nature's course. Having outlined the necessary dietary for the patient, medication is now in order. This may be divided into general and local.

The essential drugs for our consideration in the management of simple nonsurgical goiter are iodin and thyroid extract. Much has been written on the use of iodin in simple goiter, but unfortunately, in these discussions very little has been said of the therapeutic differentiation between the endemic and sporadic types of the affection.

Iodin.—The prophylaxis and treatment of endemic goiter is largely based upon the theory that there is a lack of iodin in the thyroid gland, and that, when the iodin in this organ reaches to or falls below .1 percent, goiter develops. This lack of iodin in the organ is brought about by a deficiency or absence of iodin in one or more things essential to life's processes (air, water, or food), which deficiency or absence is peculiar to the district in question. Accordingly, it has been found that the administration of the proper quantity of iodin in some form to the growing child or adult residing in these districts is successful in the prevention and treatment of goiter in the majority of cases. In general, this is true of endemic, but not of sporadic simple goiter.

In 1920, Loeb, of the Washington University School of Medicine, proved that iodin does not inhibit *compensatory* hypertrophy in the guinea pig, but that feeding with thyroid tablets has a very marked inhibiting effect. An editorial in the *Journal of the A. M. A.*, Nov. 20th, 1920, commenting upon these studies, aptly remarks: "As iodin definitely prevents or cures hypertrophic goiter, it seems clearly demonstrated that the enlarged gland condition known as endemic goiter, and compensatory hypertrophy of the thyroid are essentially different conditions." Independently of the above observations I came to this conclusion some years before through clinical studies.

In the prophylaxis of sporadic simple goiter, *i.e.*, goiter not evidently caused by geographical conditions but due to compensatory hypertrophy from physiological demands, iodin administration, contrary to the prevalent opinion, is far from routinely successful. Of the comparatively small percentage of these patients who are helped by iodin therapy, it may be assumed that their habits of life, especially dietary habits, are such as to approximate in effects upon the body those con-

ditions peculiar to geographical deficiencies. A few individuals may be so constructed as to require a greater quantity of iodin for the normal performance of the bodily functions than all the rest of humanity, and for that reason develop thyroid enlargement in the presence of an intake of what would ordinarily be considered a normal quantity of iodin. These individuals, though not living in endemic goiter districts, are scattered instances of pseudo-endemic goiter; they are cases of non-endemic iodin deficiency, the prevention of which should be based upon iodin therapy. But, to repeat, the percentage of such cases in non-goitrous districts, *i.e.*, among great numbers of sporadic simple goiters, is not as great as it is generally thought to be. To endeavor to prevent or to treat simple non-endemic goiters routinely through iodin administration yields an occasional success with a large percentage of failures, and in not an inconsiderable percentage of instances evident harm is wrought.

The following cases will illustrate the derogatory effects of iodin in sporadic simple goiter:

Miss C. G., aged 22, clerk, had goiter since the age of 14 (a year prior to menstruation). Other subjective complaints were paroxysmal attacks of migraine, each lasting 2 days, occurring once or twice a week; these were associated with nausea and vomiting. Menses began at 15. There was a previous medical history of measles, scarlet fever, and whooping cough. She was very fond of meats and was in the habit of taking 6 cups of coffee every day.

PHYSICAL EXAMINATION revealed a medium-sized symmetrical goiter which appeared to be a mixed colloid and hypertrophy of the thyroid. The patient was an unusually tall and large bodied young woman, weighing 196½ pounds, and it was therefore expected that her normal neck circumference should be somewhere between 15 and 15½ inches. The circumference of the neck at this time was 16½ inches. She was given the usual hygienic and dietetic instructions, the only medication being potassium iodid gr. ii t. i. d., increased by one grain every other day until 5 grains t. i. d. were reached, which dosage was to be continued until further orders. The patient, residing in a distant town, was able to call to see me but once in four weeks. When I saw her again a month later, the neck had increased in circumference to 17¼ inches. The patient was very much alarmed, as she believed that the goiter was beginning to choke her, and indeed, there were distinct evidences of pressure. The iodid was discontinued, and thyroid extract grains ½ was prescribed in combination with corpus luteum gr. iii, to be taken in capsule twice daily. During the ensuing month the neck circumference returned to its former measurement, and in the course of the subsequent 8 months, during which she was kept under more frequent observation than before, the neck circumference became normal, *i.e.* 15¼ inches, her normal thyroid being barely palpable beneath a neck of normal contour.

SUMMARY: A young woman of 22 with a mixed hypertrophy and colloid goiter of 8 years' duration, neck circumference of 16½ inches, was placed upon potassium iodid, which treatment resulted in an increase of the neck circumference to 17¼ inches in 4 weeks. The discontinuance of the iodid and administration of thyroid extract resulted in cure with restoration of the thyroid to normal size and a neck circumference of 15¼ inches.

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Miss A. R., age 15, schoolgirl, referred for treatment of colloid goiter which began to develop at the age of 6. There were no other subjective symptoms except occasional discomfort during swallowing and talking. Menses had not yet occurred. The mother, who accompanied the patient, was goitrous. There was a previous medical history of measles and chicken pox. She was very fond of meat, candy, spices, and coffee.

PHYSICAL EXAMINATION revealed an unusually large goiter which was symmetrical, boggy, and rather resistant to the touch. The patient was a normally built young girl whose normal neck circumference would probably be about 13 inches. Present circumference at greatest diameter of the neck was 16 inches. TREATMENT: Hygienic and dietetic instructions were given and potassium iodid gr. v., t. i. d., was prescribed. In the course of 2 months it was seen that the neck circumference had increased to 17 inches, with an accentuation of pressure symptoms, thereby alarming both the patient and relatives. The iodid was at once discontinued and thyroid ootherapy begun. It was 4 weeks before the neck circumference reached its former measurement, following which a gradual but certain reduction asserted itself, until, at the termination of the seventh month of treatment, a measurement of 13½ inches was reached. A continued observation of another 3 months was sufficient to yield a perfectly normal neck, 12¾ inches in circumference.

SUMMARY: A girl of 15 with a colloid goiter of 9 years' duration and neck circumference of 16 inches was placed on potassium iodid, following which the circumference of the neck was increased by an inch. The potassium iodid was discontinued, and thyroid ootherapy combined with other measures, resulted in a final cure of the patient, with a reduction of the circumference of the neck to normal, *i.e.*, 12¾ inches.

Did time and space permit, many other instances of similar nature could be cited, indicating that in the use of the iodids (as indeed of thyroid extract), discrimination should be exercised.

Thyroid Extract.—While iodin, not thyroid extract may be employed with advantage in the management of endemic simple goiter, *thyroid extract, not iodin*, serves the purpose in the sporadic type of the disease. To employ iodin in sporadic goiter may benefit a small percentage of patients, but in the greater majority no change in the goiter will result, and in many instances the patient will become either generally indisposed, experience an increase in the size of the thyroid, or both. Though iodin is an essential ingredient of all potent thyroid products, and though Kendall's thyroxin, the most potent of thyroid substances, seems to depend upon its 60 percent. iodin content, *it is iodin in its thyroid environment, or thyroid in its iodin environment* that is required when the thyroid apparatus, because of physiological factors, is to be relieved of its surplus burden of function. Thyroid minus iodin is impotent; with iodin it is thyroid as we know it—a substance at once a blessing and a curse in therapeutics and in sporadic goiter, depending upon whether it is used or abused. There is a "something" in thyroid substance, which is more or less specific in the prophylaxis and treatment of sporadic simple goiter. The nature of this "something" is still a mystery, but its action is unique and incomparable to anything else known in medicine.

Caution in Administration of Thyroid Extract.—Thyroid extract must be given with a keen understanding of its physiological action and the possible idiosyncrasies of the patient. All patients do not react equally to this substance. There are many reasons to account for the variable results, beneficial and otherwise, through its use, the most important of which are:

1. Those referable to the drug:
 - (a) Lack of proper standardization.
 - (b) Variations in potency of products of different firms.
 - (c) Lack of potency because of age of the product.
 - (d) Formation of ptomaines due to age of the product.
2. Those referable to the patient:
 - (a) Natural susceptibility to the drug.
 - (b) Natural insusceptibility to the drug.
 - (c) The occasional uncertainty of the presence or absence of an impending hyperthyroidism with or without Graves' disease.

Unfortunately, there is no such thing as *perfect* standardization of thyroid extract. An examination of a sample from each of the numerous firms manufacturing thyroid extract yields startling variations in potency, from zero to 100 as the maximum. Again, the potency varies at different times with the same firm, this probably depending upon variation in the raw product received by its chemists. Furthermore, thyroid substance may be exposed to the deterioration of time prior to its manufacture into powder form, and also subsequent to that time. Many druggists, not cognizant of the importance of dispensing very fresh organic products, use it after having kept it on their shelves for weeks, months, and occasionally years. Not only do the iodin and other potent factors disappear during this time, but not infrequently certain ptomaines develop which may give rise to marked toxic symptoms when administered, which symptoms are in some instances construed to be evidences of hyperthyroidism. A few such cases of ptomaine poisoning have come to my attention. The doctor had best anticipate the possibilities when prescribing thyroid extract by placing upon the prescription after this drug the word "fresh" or "recent" underlined, with an exclamation mark or two. In one prescription upon which I placed the word "recent" after the drug, the pharmacist phoned me asking in all seriousness whether this was the name of a new firm manufacturing endocrine products. This is probably due to the overnight crops of manufacturing houses undertaking the manufacture of so important a therapeutic product. Furthermore, I place upon my prescriptions, in parentheses, the name of what I believe to be the most reliable firm manufacturing thyroid extract. Further to safeguard matters, I request the patient to have the prescription filled at the most reliable drug store he knows of.

It is very difficult and at times impossible to decide in advance which patient will react promptly and which slowly to thyroid extract. Every patient is a law unto himself, and individualization must indeed be observed when prescribing thyroid extract. One patient may require but $\frac{1}{8}$ of a grain daily to procure the desired results; another, not less than 5 grains; here is a patient in whom $\frac{1}{4}$ grain daily asserts itself in slight restlessness and increased heart action; there is an adolescent in whom this result is brought about through the administration of one grain daily. Again, what has at one time been the proper dosage in a given patient becomes at another time a full physiological or even a toxic dose. Thyroid extract possesses, like digitalis, cumulative tendencies. Unless this is borne in mind, the patient may be brought to a dangerous state of hyperthyroidism, with or without exophthalmic goiter. Of course, we cannot know what dosage brings about evidences of accumulation, and when it will occur. This is determined through frequent observation of the individual—not less often than once a week during the administration of the drug. In one patient the proper therapeutic dose may begin to exert slight toxic effects within a few weeks; in another, in three or four months. If, in a given patient, what is thought to be the proper dose gives rise to uncomfortable symptoms within a week or two, the dosage was too large at the start and should have been smaller, as the patient has an extreme susceptibility to the effects of thyroid extract.

Thyroid extract is administered on the basis of substitution. On the assumption that the organ is incapable in its normal size of supplying the body with the required quantity of hormone, thyroid extract is given to supplement the quantity supplied by the patient's gland. The deficiency in some patients is little, in others more. Just how deficient in function is a given thyroid gland no one can tell in advance. The therapeutic test, *i.e.*, the cautious administration of a reliable thyroid extract, is the only guide.

When thyroid reaches the intestines it is split up into amino-acids and thyroxin. The latter enters the circulation, thus resting the thyroid gland. The organ, relieved for a sufficient time of the strain of function or over-function, soon loses its hypertrophy, becoming normal in size. With the elimination of causal factors (in the absence of myxedema), there occurs sooner or later a gradual restoration of equilibrium between demand and supply of thyroid hormone so that thyroid administration may be gradually withdrawn without fear of a returning hypertrophy of the patient's gland. The continued administration of thyroid at this time is unnecessary and hazardous as it is no longer needed and may lead to thyrotoxemia. All that seemed necessary was a physiological adjustment through artificial means, and a natural adjustment followed. The duration of this process varies from a month to a year, depending upon individual circumstances.

Contraindications to Thyroid Opotherapy.—In this connection, let it be emphasized that if on examination of the thyroid gland a thrill, bruit, or both are elicited, thyroid extract is contraindicated. Again, if in a given case some time after the beginning of thyroid opotherapy, a thrill or bruit over the thyroid is discovered, the drug must be discontinued at once. Under these circumstances, to administer or to continue administering thyroid extract is to imperil the future of the individual. In this relation, it is at times difficult to recognize in advance the uncommon individual whose thyroid is on the verge of becoming definitely hyperplastic, a pathological status in which thyroid extract is never to be administered. However, many such borderline cases abound which could be recognized by certain earmarks elsewhere in the body. In the presence of a normal basal metabolism, the quinin test described in the chapter on clinical tests may assist in discriminating the individual. To amplify these remarks, we might make this generalization: Persons in whom there is an undue heart hurry on slight exertion, a fine fibrillary tremor, and an evident degree of mental excitability, had better not be given thyroid extract, even though the thyroid gland presents no hyperplasia on physical examination. Such a person may develop a thrill and bruit at any time and must therefore be regarded as a pre-Graves' disease subject. It is evident, then, that to give thyroid extract to all patients presenting an enlarged neck, even though there are no obvious signs of exophthalmos and rapid heart, is unscientific and dangerous. Each patient must be carefully studied prior to prescription writing. A careful diagnosis must be made not only of the "lump" on the neck, but also of the type of individual, and if it is decided that thyroid extract is to be administered, frequent examination to determine the physiological results should be made.

Thyroxin, though eminently successful in the treatment of cretinism, and despite good reports of its use in simple, especially colloid goiter, is to be employed with caution, if at all. I do not favor the use of such a potent substance intravenously, as advocated by a few observers. I have administered thyroxin by mouth and have not seen any advantages over a good thyroid extract. In fact, symptoms of thyrotoxemia are easily produced by thyroxin administration even in minute doses, while this is not occasioned in the same patients when thyroid extract is administered in the proper dosage.

Method of Administration of Thyroid Extract.—Let us now discuss prescription writing. The dose to be prescribed will depend among other things upon the age of the patient, the tolerance to the drug, and the duration and size of the goiter. Assuming that the patient in question is an adolescent female with a moderate sized colloid goiter of one or two years' duration, or a simple hypertrophy of two or three years' duration, it is well to begin with thyroid extract gr. $\frac{1}{8}$ administered in tablet or capsule form at bed time. If, at the end of the first

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week, the drug seems well tolerated, the dose may be administered twice a day, or gr. $\frac{1}{4}$ may be given at bed time only. If, after this is continued for another week or two, there are no evidences of intolerance, but, on the contrary, the patient seems not to present any evidences of having taken thyroid extract, the dosage may be still further increased, giving the substance either in dose gr. $\frac{1}{8}$ t.i.d. or gr. $\frac{1}{4}$ night and morning, or gr. $\frac{1}{2}$ at bed time. The manipulation of dosage and the frequency of administration depend upon the good judgment of the medical attendant. I have found that the dosage tolerated by the patient is somewhat larger *per diem* if the substance is given in one dose at bed time. This is probably due to the fact that the patient retires at once, and the possible somatic exciting influence of the thyroid is thus obviated by sleep.

In younger patients, diminished tolerance, larger goiter or goiter of greater duration than that just discussed, the dosage and frequency of administration must, of course, be correspondingly altered. There are patients in whom there is a lessened tolerance than usual, and others in whom, because of an unusual size of the neck or of unusual duration, it is desirable to push the drug to a point of accentuated physiological action. This may be done on the condition that exceptional care be taken by frequent observation of the patient and by certain combinations with other drugs which serve to "guard" the patient to a certain degree against the toxic effects of thyroid extract.

In a patient, for instance, whose normal neck circumference should be 13 inches, but whose goiter increased the circumference to 16 or 17 inches, *full doses* of thyroid extract may be required. This presupposes that the medical attendant is reasonably certain that he is not dealing with a hyperplasia of the thyroid merging into toxicity, or with an adenoma of distinctly surgical nature. Assuming, then, that we have a patient before us whose neck circumference is 3 or more inches in excess of the normal, and in whom we are dealing with a nonsurgical goiter, therapeusis is begun in the usual fashion as herein outlined. The dosage of thyroid extract at first, perhaps, gr. $\frac{1}{4}$ daily, is increased in the course of a month to gr. $\frac{1}{2}$, and in the course of the ensuing month to gr. i to ii. If, at this time, the thyroid has evidently been reduced $\frac{1}{2}$ inch or more in circumference, the dosage need not be increased, but continued while the medical attendant awaits further reduction and final cure of the case. If there has been no reduction and simultaneously no evidences of thyroid intoxication, the dosage of thyroid extract may be further increased to gr. iii, iv, or v daily. This dosage should be increased very gradually, perhaps by $\frac{1}{2}$ gr. every week or two till there is slight toxicity. Full physiological effects amounting to mild toxic symptoms are occasionally to be provoked in isolated cases which present opportunity for careful observation and in which the primary diagnosis is assured. A thorough experience in this branch of medicine

is a prerequisite to such an undertaking. Thus, a patient such as aforementioned, whose heart rate was formerly 70, may reach a rate of 90 or even 100, but if we succeed in reducing the size of the thyroid substantially, we have produced great good by means of a little harm. A discontinuance of the drug at this time and the proper institution of other remedial measures antagonistic to hyperthyroidism will bring the patient promptly back to his former health. Also a discontinuance of thyroid opotherapy at this time, if the neck circumference has already been markedly reduced, will mean a continued reduction in its size, the thyroid gland continuing on its progress to normal while the patient is ridding himself of the induced hyperthyroidism. When the heart rate has again become normal, thyroid opotherapy may be continued, but with much smaller doses than before, not necessarily to the point of hyperthyroidism, since the patient has become sensitive to the drug. This treatment is continued for 2 or 3 months past the time of the restoration of the neck to normal.

The institution of a mild hyperthyroidism in patients of this sort is not often necessary, but in unusual instances in which it seems essential, it must be done guardedly. During this process, the patient's weight must be maintained at least at the normal figure, or better still, above normal, by hyperalimentation; and certain other drugs calculated to offset toxicity and to maintain the body resistance at its best are to be employed.

"Guarding" and Combining Thyroid Extract.—In patients requiring the rapid or intense therapeutic action of thyroid extract, a larger dosage may be administered, combined with such substances as are known to have antagonistic physiological effects. This may seem paradoxical, but though certain substances are theoretically antagonistic to thyroid extract, the opposition seems only to direct itself to untoward effects of thyroid administration and not to an obvious degree of full physiological influence. Combinations of known physiological antagonists are occasionally administered in other fields of medicine. Thus, morphine and atropin, digitalis and aconite, sodium bromide and nux vomica; and numerous other apparently opposed drugs are frequently combined with a definite purpose. Corpus luteum and pancreatin are theoretically opposed to the thyroid, but the combination of the latter with one or both of the former in no way interferes with the principle of resting the patient's thyroid gland, while at the same time the probability of toxic effects through thyroid administration is reduced. Moreover, despite theoretic antagonism, the combination of thyroid with corpus luteum is frequently observed to be a synergistic one, as it seems in great measure to overcome and arrest certain etiologically related pelvic disorders or dysfunction, thus diminishing the strain on the patient's thyroid gland. A patient suffering with unusual discomfort during menstruation certainly feels relieved with such a combination.

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Accordingly, let us examine a few prescriptions applicable to some of these patients:

Formula 1: Rx Ext. glandulæ thyroidæ gr. $\frac{1}{8}$ to $\frac{1}{4}$
Corpus luteum gr. ii
In caps. i. Mitte No. XX.
Sig.: 1 capsule 2 or 3 times a day.

or Rx Ext. glandulæ thyroidæ gr. $\frac{1}{4}$ to i
Formula 2: Corpus luteum

Pancreatin a.a. gr. iii
In caps. i. Mitte No. XX.
Sig.: 1 capsule once or twice a day.

or Rx Ext. glandulæ thyroidæ gr. ss to ii
Formula 3: Corpus luteum gr. v.

In caps. i. Mitte No. XIII.
Sig.: 1 capsule at bed time.

Unsatisfactory sleep, if a previous complaint or if a result of having taken thyroid extract, may be rectified by the inclusion in the formula of veronal or luminal, as for example:

Formula 4: Rx Ext. glandulæ thyroidæ gr. ss to ii
Corpus luteum gr. v.
Veronal gr. ii vel luminal gr. ss
In caps. i. Mitte No. XII.
Sig.: 1 at bed time.

In case of constipation, which may indeed be etiologically related to the thyroid enlargement, it is imperative that efforts be made to overcome it. This may easily be done by including in the usual capsule taken once, twice, or t.i.d., such substances as phenolphthalein, extract of cascara, or aloin. The latter is by far the preferable substance to employ, but because of its tendency to produce abdominal discomfort if taken during the day, it had best be incorporated into the usual capsule intended to be administered at bed time. Thus, the following prescription will meet these indications:

Formula 5: Rx Ext. glandulæ thyroidæ gr. ss to ii
Corpus luteum
Pancreatin a.a. gr. iii
Aloini gr. $\frac{1}{10}$ to $\frac{1}{3}$
In caps. i. Mitte No. XIII.
Sig.: 1 capsule at bed time.

In patients requiring improvement in appetite through a medicinal tonic, and especially those who are suffering with a degree of secondary anemia, a capsule containing thyroid extract plus other indicated in-

gredient may be given. For instance, in a female, age 20, who presents herself for treatment of a medium sized colloid goiter or thyroid hypertrophy, and who is undernourished, anemic and constipated, the following formula (with variations in dosage of ingredients according to indications) may be employed:

Formula 6: Rx Ext. glandulæ thyroidæ gr. $\frac{1}{8}$ to $\frac{1}{4}$
Corpus luteum gr. ii
Calcii glycerophos. gr. v.
Ferri arsenias gr. $\frac{1}{10}$
Ext. cascara gr. $\frac{1}{8}$ to i
In caps. i. Mitte No. XX.
Sig.: 1 capsule 3 times a day.

or
Formula 7: Rx Ext. glandulæ thyroidæ gr. $\frac{1}{8}$ to $\frac{1}{4}$
Corpus luteum gr. ii
Calcii glycerophos. gr. iv
Massa ferri carb. gr. ii
Arseni trioxidi gr. $\frac{1}{40}$
Aloini gr. $\frac{1}{10}$ to $\frac{1}{6}$
In caps. i. Mitte No. XX.
Sig.: 1 capsule 3 times a day.

Assuming that the hypothetical patient aforementioned is not only undernourished, anemic, and constipated, but is also suffering with dysmenorrhea, hyperacidity, and insomnia, a combination of clinical complaints quite common in young adults, the following formula is suggested:

Formula 8: Rx Ext. glandulæ thyroidæ gr. $\frac{1}{8}$ to $\frac{1}{4}$
Corpus luteum gr. ii
Ferri arsenias gr. $\frac{1}{10}$
Calcii glycerophos. gr. v.
Luminal gr. $\frac{1}{8}$
Mag. oxidi ponder. gr. viii to xii
In chart. i. Mitte No. XX.
Sig.: 1 powder $\frac{1}{2}$ hour after meals, 3 times a day.

Though iodin has been discussed as a substance *not* to be employed routinely in sporadic simple goiter, there are patients in whom, administered in *combination* with thyroid extract, iodin seems to be of distinct service, though alone it is open to the objections mentioned. The admixture of iodin during thyroid administration renders the latter more capable of therapeutic effects, and therefore a smaller dosage of thyroid may be given. In instances of simple hypertrophy or colloid goiter in which it appears desirable to combine thyroid extract with iodin, I occasionally find the following formulæ of service:

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Formula 9: Rx Ext. glandulæ thyroidæ gr. $\frac{1}{4}$
Hydrarg. protiodidi gr. $\frac{1}{16}$
Calc. glycerophosph. gr. v
In caps. i. Mitte No. XX.
Sig.: I capsule night and morning.

or Rx Ext. glandulæ thyroidæ gr. $\frac{1}{8}$ to $\frac{1}{4}$

Formula 10: Rx Corpus luteum gr. ii
Hydrarg. protiodidi gr. $\frac{1}{12}$
Calc. glycerophosph. gr. v
Ext. cascara gr. $\frac{1}{2}$
In caps. i. Mitte No. XX.
Sig.: 1 capsule before each meal 3 times a day.

I find that the protiodide of mercury is quite satisfactory combined in prescription with thyroid extract and other ingredients. If this produces gastric irritation, I administer, instead, the tincture of iodin, one or two drops in a half tumblerful of water employed to wash down the capsule, as in the following:

Formula 11: Rx Ext. glandulæ thyroidæ gr. $\frac{1}{8}$
Corpus luteum gr. ii
In caps. i. Mitte No. XX.
Sig.: 1 capsule night and morning to be washed down by a half tumblerful of water containing 1 or 2 drops of tincture of iodin.

I have never seen any mental or gastric aversion to the tincture of iodin administered in this fashion.

LOCAL MEASURES

In a goodly percentage of nonsurgical goiters, certain local measures, though not to be employed as mainstays, are often useful supplements to internal medication and other measures in treatment. The first of these to be mentioned is *medication*. I have found the following prescriptions of use:

Formula 12: Rx Tr. Iodin fl. dr. $\frac{1}{2}$ to i.
Ungt. Pot. Iodid q.s. ad. $\frac{3}{2}$ ii
M. et fiat ungt.

Sig.: Employ locally at bed time; apply a quantity of ointment equivalent to the size of a split pea over the thyroid, rubbing the ointment in thoroughly until it is absorbed.

or Rx Menthol gr. ii

Formula 13: Rx Camphor gr. v
Tr. Iodin fl. dr. iii
Tr. Belladonna q.s. ad fl. oz. i
Sig.: Paint the goiter lightly at bed time, or every other night if the skin becomes tender.

I regard the ointment first mentioned as the more serviceable of the two formulae, as it is rarely irritating, and it does not discolor the skin. Let it not be understood that the above local formulæ are *essential*. They are merely useful or supplementary; they do no harm in combination with other measures in treatment; employed alone, they possess little if any virtue, but if combined as supplements with other more substantial measures, they expedite results.

Electricity.—The various currents have varying local and general effects upon these patients. I find the *x-rays* useless in these simple nonsurgical goiters, *i.e.*, simple hypertrophy and colloid goiter. Since simple unencapsulated goiter is a compensatory swelling because of demands for the thyroid hormone elsewhere in the body, the destructive effect of x-ray treatment is contraindicated and is apt to lead to myxedema. The most useful forms of electricity, if electricity is to be employed at all, are the galvanic and the static currents. *Galvanism* applied over the thyroid swelling in the form of a moistened sponge is, I believe, a good supplement to other more general substances employed. The sponge electrodes may be applied on each side of the goiter simultaneously, or the anode may be applied over the nape of the neck, and the cathode over the thyroid. The sponge applied over the thyroid should be moistened with sodium bicarbonate solution or with an aqueous solution of potassium iodid. I usually administer it during a period of 10 minutes, once or twice a week. The strength of the current is usually about 10 milliamperes, not great enough to cause discomfort or blistering, but sufficient to yield a reddening of the skin over the thyroid at the termination of the period of treatment. The *static wave current* is, I feel, an important adjuvant. The patient is seated on an insulated platform, and the current is administered through a moist sponge applied to the thyroid. The negative pole of the machine is grounded, the positive is applied to the goiter. The posts of the static machine are separated at such a distance that the spark occurs 4 to 8 times per second, requiring a spark gap of 3 to 6 inches. Most patients find this treatment quite tolerable, but there are individuals in whom it may be necessary to administer it much weaker at first. These treatments may also be administered daily, or once, twice, or three times a week. I find it useful to alternate the static wave with galvanism in certain instances. We must emphasize that electricity at its best is an excellent supplement to more substantial measures employed in the management of goiter patients. If properly applied, it is harmless, and while in most patients it may not do good, in many instances the period of general treatment is considerably abbreviated.

Mechanical Pressure.—Flexible collodion, adhesive plaster, and other contrivances for the purpose of mechanically compressing the enlarged thyroid with a view to reducing its size to normal have been tried from time to time by the older observers, but these measures are

of questionable value. Theoretically, it would seem that in instances of colloid goiter and of hyperplastic goiter—thyroid enlargements which to an extent resemble a filled sponge—mechanical compression properly applied would serve to express the pathological contents responsible for the enlargement of the organ and would thus serve to train the gland to maintain its normal size.

With this in view, I have contrived what may be termed a *goiter binder*¹ which I have been employing with satisfaction. The principle adopted is that of the surgical binders for splanchnoptosis on a miniature scale. The patient must, of course, be properly fitted for individual needs, for each neck presents its own size and shape. The following illustration describes this apparatus:

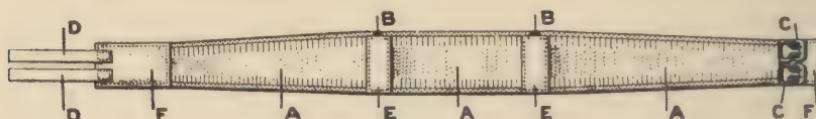


FIG. 33.—Goiter binder. A. Elastic web; B. Supporting stays; C. Buckles; D. Straps; E. Stay sheaths; F. Reinforcements for buckles and straps.

It must be well fitted by the maker, so that when applied with a fair degree of firmness no discomfort is experienced by the patient. It is worn during the night, which constitutes a sufficient period of time to serve its purpose. The patient must be warned not to apply it too tightly, for the degree of pressure must not be sufficient to interfere with comfort or sleep. If a salve is employed the binder may be applied immediately thereafter, with a small portion of soft flannel placed over the skin first, so that the binder, which is made essentially of rubberized cloth, will not irritate the skin.

The Duration of Treatment of simple parenchymatous and colloid goiter depends upon the age, the idiosyncrasies of the patient to drugs, and the duration and size of the thyroid swelling. In a goiter of moderate size, of 1 to 3 years' duration, treatment should yield tangible results within 3 months, at which time the neck circumference should show a reduction of from $\frac{1}{8}$ to $\frac{3}{8}$ of an inch. This result may be accomplished in a month or two. Again, in large goiters undergoing growth, there may be no improvement within 3 or 4 months, and just as both doctor and patient are about to become discouraged, the goiter may undergo rapid reduction in size, and the neck may assume the normal

¹This is my own contrivance; I am not desirous of commercializing it, and I trust that no one will patent it. The binder is contraindicated in surgical goiter. It is of service only in the 4 types of thyroid enlargement designated as non-surgical goiter, *i.e.*, simple hypertrophy, colloid goiter, puberty hyperplasia, and the hyperplastic thyroid of exophthalmic goiter.

appearance at the termination of the sixth or seventh month of treatment. Ordinarily, I would state that those simple goiters which are amenable to nonsurgical treatment—even goiters of several years' duration—are cured within from 3 to 12 months, the great majority of necks becoming normal within 7 months of properly applied treatment.

Permanency of Cure.—The goiter having disappeared and the neck being restored to normal size and shape, the question naturally arises as to whether the cure is permanent. While it would seem that a person having had thyroid enlargement may be more susceptible to goiter than the average individual, especially in view of the fact that heredity plays an important rôle, in my experience cure is permanent in patients who do not discontinue treatment abruptly. Of course, there are instances in which the diagnosis of nonsurgical goiter is not entirely correct. But in experienced hands, the percentage of error is negligible, and even the occasional instance in which slight adenomatous or cystic changes have escaped the attention of the diagnostician, the treatment as here outlined is productive of great good, since, though the neck may not be restored entirely to normal, it is sufficiently improved or so nearly normal to render great satisfaction to the patient. But in the vast majority of cases, at least 95 percent., the diagnosis of nonsurgical goiter is easily made by the history and physical examination, as well as by previous experience of the medical attendant. The patient on being discharged is instructed to return once in two or three months during the ensuing year for observation regarding permanency of cure. During the year of observation minute doses of thyroid extract may be continued, say grains $\frac{1}{8}$ to $\frac{1}{4}$ daily or every other day. This is not essential, but it safeguards the patient's thyroid gland for yet awhile. Also, when passive observation is begun the patient is warned not to transgress in hygienic and dietetic instructions already given. In brief, the acts of life are so adjusted as to place the least possible strain upon the thyroid, this constituting what I term an "anti-goiter existence." In most instances I give the patient a typewritten list of instructions as a guide to future welfare. Patients so treated are cured permanently. I have had no recurrence of thyroid enlargement following the nonsurgical management of true nonsurgical goiters.

RESULTS OF NONSURGICAL TREATMENT OF NONSURGICAL GOITER



FIG. 34.—Parenchymatous hypertrophy of the thyroid; several years' duration; circumference of neck 14 inches.



FIG. 35.—Same patient as in Fig. 34 following nonsurgical treatment. Neck is normal with circumference of 13½ inches.



FIG. 36.—Parenchymatous hypertrophy of 8 years' duration; recurrence after each of 2 thyroidectomies; circumference of neck 13½ inches.



FIG. 37.—Same patient as in Fig. 36, as a result of nonsurgical treatment; disappearance of goiter, with reduction of circumference of neck by one inch.



FIG. 38.—Thyroid hypertrophy of menopause with hyperthyroidism of several years' duration; neck circumference 14½ inches; heart rate 100; hypertension and general weakness, tremor, loss in weight.

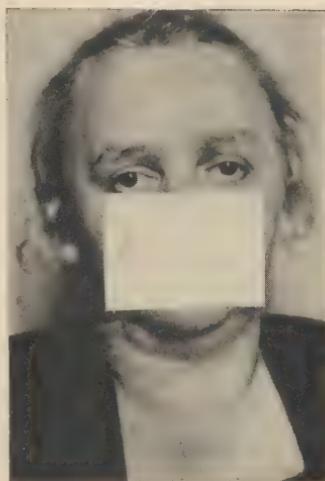


FIG. 39.—Same patient as in Fig. 38 as a result of treatment; neck circumference 14 inches with normal thyroid (patient now presents a fold of fat at site of previous goiter); complete recovery from evidences of hyperthyroidism.



FIG. 40.—Persistence of thyroid hypertrophy of adolescence, 10 years' duration; circumference of neck 13½ inches.



FIG. 41.—Same patient as in Fig. 40 after treatment; neck circumference 12½ inches with disappearance of goiter.

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Figs. 42 and 43.—Puberty hyperplasia of 8 years' duration; circumference of neck 16% inches.



Figs. 44 and 45.—Same patient as in Figs. 42 and 43, as a result of treatment; circumference of neck reduced by 1½ inches with disappearance of goiter.



FIG. 46.—Hypertrophy of adolescence, in girl of 15. Neck circumference $13\frac{1}{4}$ inches.



FIG. 47.—Same patient as in Fig. 46 after 6 months' treatment. Normal thyroid with reduction in neck circumference by $\frac{1}{8}$ of an inch.



FIG. 48.—Thyroid hypertrophy of 2 years' duration in girl of 15. Circumference of neck $13\frac{1}{2}$ inches.



FIG. 49.—Same patient as in Fig. 48 after 6 months' treatment. Disappearance of goiter with neck circumference reduced to $12\frac{1}{4}$ inches.



Figs. 50 and 51.—Colloid goiter of 3 years' duration in girl of 15; circumference of neck $14\frac{1}{2}$ inches.



Figs. 52 and 53.—Same patient as in Figs. 50 and 51 as a result of treatment. Circumference of neck reduced by $2\frac{1}{4}$ inches with disappearance of goiter.—During the 7 months' treatment the patient gained 20 pounds in weight.



Figs. 54 and 55.—Mixed parenchymatous and colloid goiter of 8 years' duration with beginning hyperthyroidism in girl of 15; circumference of neck $16\frac{1}{2}$ inches.



Figs. 56 and 57.—Same patient as in Figs. 54 and 55 after 7 months' treatment. Reduction in circumference of neck by 4 inches, with disappearance of goiter and of hyperthyroidism.

CHAPTER VII

PUBERTY HYPERPLASIA

SIMPLE parenchymatous hypertrophy and colloid goiter are enlargements of the thyroid gland indicating a degree of thyroid insufficiency in which the organ, in an attempt at compensation, undergoes enlargement.

Puberty hyperplasia, on the other hand, is due to causes mentioned in the production of simple hypertrophy *in an individual with an inherited neuro-endocrinopathy*. Premenstrual and menstrual conditions, the stress of school work, adolescence, and infections, instead of producing a mere need for more thyroid secretion, stimulate the sympathetic nervous system and the adrenals into a reflex hyperthyroidism of varying degree. Indeed, we may observe a mild form of a widespread neuro-endocrine dysfunction amounting to a pre-Graves' or even a Graves' status of larval form in these persons.

Symptomatology.—Ordinarily, these youths and maidens with puberty hyperplasia are an interesting type. The reduced emotional threshold and the aptitude for mental activity and the arts may stamp the male as an embryo Shelley, a Michael Angelo, or a Paganini, and the female a Patti, or a Sarah Bernhardt. There is a strong attraction for the opposite sex, and love and romance constitute a great part of their mental activities. These persons are usually healthy colored and moist of skin, with brilliant eyes. They often possess a fine tremor, and there is a soft fullness of the thyroid—"the swan neck" of the bards of old, often amounting to a definite sized goiter. There are usually no subjective complaints other than an out-of-breath feeling following moderate or slight exertion. Ordinarily these subjects may be exhilarated by their peculiar make-up into an undue sense of well being. These individuals are further described in the chapter on the prevention of Graves' disease.

The course of this condition varies with circumstances. Some of these subjects make a spontaneous recovery within from several months to 2 or 3 years. A goodly percentage progress more or less gradually with or without an acute exciting cause, toward the Graves' disease syndrome. In all subjects of puberty hyperplasia whether very mild or quite apparent, a cause recognized as capable of instigating Graves' disease is apt to transform the individual rather suddenly into a subject of this affection. An automobile, trolley or train accident, disappoint-

ment in love, or the death of a dear relative, and the syndrome of the disease may assert itself, with the formation of thrill and bruit over the thyroid, tachycardia, accentuation of the tremor, bulging eyes, and all the appearance of frozen fright.

Diagnosis is important, for whereas in hypertrophy and colloid goiter there are often evidences of thyro-adrenal and sympathetic *hypofunction*, in puberty hyperplasia there is a symptomatology of neuro-endocrine instability with thyro-adrenal *hyperfunction*. The youth of



FIG. 58.—Puberty hyperplasia.—A sister of this patient suffered with severe exophthalmic goiter.



FIG. 59.—Puberty hyperplasia in a young man with an artistic temperament.

the patient, the soft, symmetrical though moderately sized enlargement of the thyroid (without thrill or bruit); the high-colored soft, moist skin; sparkling eyes, fine tremor, the tendency to tachycardia and dyspnea on slight exertion; and the history of physical and mental over-alertness render the diagnosis a simple task.

The following tabulation will assist in the differential diagnosis between simple hypertrophy and colloid goiter on the one hand, and puberty hyperplasia on the other:

Simple Hypertrophy and Colloid Goiter

1. No neuro-endocrinopathy.
2. No over-alertness of body and mind.
3. No excessive moisture of skin, dermographia, tremor, or sparkle in the eyes.

Puberty Hyperplasia

1. Inherited neuro-endocrinopathy common.
2. Over-alertness of body and mind.
3. Tendency toward excessive moisture of skin, dermographia, tremor, and sparkle in the eyes.

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Simple Hypertrophy and Colloid Goiter

4. No undue tendency to rapid heart and dyspnea.
5. Thyroid opotherapy indicated.
6. Quinin test negative.
7. Basal metabolism normal or below normal.

Puberty Hyperplasia

4. Tendency toward rapid heart and dyspnea on slight exertion.
5. Thyroid opotherapy contraindicated.
6. Quinin test usually positive.
7. Basal metabolism varies from normal to plus 20 or more.

Prophylaxis and Treatment are discussed in other chapters, especially in the remarks on the prevention of exophthalmic goiter. We must here emphasize that thyroid opotherapy should never be considered in the prophylaxis or treatment of these patients, as this drug may serve as the exciting cause in the development of Graves' disease. Should puberty hyperplasia merge into the Graves' syndrome, early, persistent treatment as outlined in another chapter yields prompt results and an eradication of the previous susceptibility to the affection.



FIG. 60.—Puberty hyperplasia of 9 years' duration merging into exophthalmic goiter. Circumference of neck 14½ inches; weight 113 pounds; pulse rate 124.



FIG. 61.—Same patient as in Fig. 60 after 10 months of treatment. Circumference of neck 13½ inches with disappearance of goiter. There is a gain of 26 pounds in weight; pulse rate is 72. (Patient continued working while under treatment.)



FIG. 62.—Puberty hyperplasia. Circumference of neck 15½ inches; weight of patient 122 pounds.



FIG. 63.—Same patient as in Fig. 62 after 5 months of treatment. Neck circumference is reduced by one inch with disappearance of goiter. There is a gain of 23 pounds in weight. (This patient's father was discharged cured of exophthalmic goiter in 1917.)

CHAPTER VIII

ETIOLOGY OF EXOPHTHALMIC GOITER

THE etiology of this disease has for many years been the object of more speculation than that of any other syndrome known to medicine. The manifestations of the disease seem interwoven with all the endocrine organs, the vegetative nervous system, the central nervous system—in fact, with every physical and mental tissue and function of the economy. Moreover, the complexity of the questions involved is intensified by the innumerable variations in the clinical pictures observed; so that each patient must be studied as a distinct entity, apart from all the rest.

It must be emphasized that we shall here consider not toxic adenoma or the so-called "secondary toxic goiter," but true exophthalmic goiter or Graves' disease.

TERMINOLOGY

Exophthalmic Goiter is the most common term employed to designate the syndrome and is responsible for some of the prevailing confusion in the understanding of the disease. The term is unfortunate, since (1) goiter and exophthalmos often occur late and are frequently absent, and (2) it stresses goiter as etiologically responsible for the disease, a conception inconsistent with prevailing opinions entertained by students of this affection.

Hyperthyroidism is also a misleading term, for though a percentage of clinicians, especially surgeons, still entertain the idea that the disease is due to thyroid hyperactivity, many experimental and clinical facts contradict this view. Thyroid hyperfunction exists as a factor in the syndrome of the disease, but it is an *incidental* factor—a link in the chain of events constituting the syndrome. As Plummer and others have well emphasized, and I have frequently stressed, hyperthyroidism is responsible for all symptoms observed in *toxic adenoma*, but in exophthalmic goiter it constitutes a fraction of the clinical picture and is probably a reaction defending the individual against toxins originating elsewhere in the body. So that the term hyperthyroidism is not a desirable synonym for this syndrome.

Graves' Disease is probably a most desirable term, since there is really no objection to the application of the name of a pioneer to a disease he has studied and described. Though Graves of Dublin de-

scribed it in 1835, others, at an earlier and later date, did likewise. The question as to whom is due the credit for first having described this disease is still unsettled. A. Souques, a collaborator in a recent book, suggests that the honor has been attributed variously to Saint-Yves, Demours, Flajani and Testa, but that Parry described the first recorded cases of exophthalmic goiter. Although Basedow and Graves had already written on the subject, the first French observations on this disease were published by Charcot who obtained his knowledge of the syndrome from a foreign student whom he was teaching.

Parry's Disease is the term employed by some, because in 1786 Caleb Parry of Bath called attention to a series of symptoms corresponding to this syndrome, and to him, according to Osler, belongs the credit of priority.

Basedow's Disease or "**Die Basedow'sche Krankheit**" is the term employed by the Germans because Basedow of Germany described the disease in 1840.

Flajani's Disease is the term employed by Italians because in 1802 Flajani, of Italy, described some of the symptoms.

Toxic Goiter implies the constant existence of goiter and is a loose term. Moreover, it leads to the erroneous inference that the disease is essentially one of goiter, and is local, not general, in etiology and clinical manifestations.

Hyperplastic Goiter, though a more acceptable term than the preceding, is open to the same objections.

Dysthyroidism, a term indicating a departure from the normal in the quality and quantity of thyroid substance within the bodily structures, seems justified on the basis of the generally accepted conclusion that some of the manifestations of the disease are occasionally associated with those of hypothyroidism. However, here, too, the special emphasis on the thyroid gland seems inconsistent in the presence of evidences of a more widespread pathogenesis.

The term *thyrotoxicosis* is open to the same objections as the terms toxic goiter and hyperthyroidism.

Since, however, the term exophthalmic goiter, though inconsistent, is commonly employed as indicating the syndrome under discussion, and since Graves' disease is the synonym most commonly employed in English speaking countries, we employ these terms, namely, exophthalmic goiter and Graves' disease, interchangeably in this book, to represent the syndrome described in our remarks.

The precise etiology of the disease is still unknown. Despite the incessant labours of men devoting much of their lives to this field, who can tell how near we are to clearing up endocrine and autonomic physiology and pathology? Is Graves' disease an affection originating in single or multiple glandular structures? Do the palpitation and the tachycardia, the trembling of all the muscles of the body, the protruding

eyeballs, the cold, clammy skin, the extreme restlessness, the nervous diarrhea—all these constituting the picture of fright—indicate that the cause lies in a disturbance of the emotional balance with a secondary endocrinopathy, or is it in a derangement of the sympathetic nervous system? Are the suprarenal glands and pituitary body innocent bystanders in the development of the syndrome, or is the entire picture instigated through some specific auto intoxication from the digestive organs? What part does heredity play in the development of the disease? These and dozens of other questions may be asked, but the answers are not forthcoming in spite of the vast amount of literature already written on this subject. That exophthalmic goiter and other diseases, eminently diabetes mellitus, arthritis deformans, and occasionally epilepsy, are frequently seen to follow a sudden shock to the emotions, especially fright, has led many to believe that loss of emotional balance is in a large measure responsible for the onset of exophthalmic goiter. To add to the perplexity of this question, we read reports of instances of spontaneous cure of advanced cases of exophthalmic goiter, and the patient, after having gone the rounds of hospitals and physicians, and having given up all hope of cure, suddenly finds himself on the high road to recovery. Still more mysterious is the rare instance of recovery from the disease following an added shock superimposed upon the existing syndrome. I know of a woman whose swollen thyroid and other symptoms so preyed on her mind that she became a subject of occasional attacks of suicidal mania. In one of these attacks she seized a large knife and attempted suicide by cutting her throat. But the goiter acted successfully as an insulator, and the great vessels of the neck were unimpaired. She slashed herself again and again, only succeeding in severing several vessels coursing through the peripheral portion of the goiter, which caused her to fall to the floor in a faint from pain and loss of blood. When discovered, she was taken to a hospital, where the wounds healed kindly by first intention. At the same time it was noticed that the swelling which had existed for several years was becoming smaller. Soon the mass was seen to shrink with great rapidity, and in three months it was gone, with amelioration of all other symptoms of the disease.

A FEW POSSIBLE PREDISPOSING FACTORS

Heredity.—An inherited neuro-endocrinopathy has often been demonstrated in these patients. In a series of 82 cases analyzed by Packard, there was a definite hereditary tendency in 6 percent. Rosenberg reports a family in which a grandfather, father, two aunts, and two sisters were afflicted with the disease. Oesterreicher reports eight of a family of ten suffering with the syndrome. Bumstead reports a family in which four sisters suffered with Graves' disease of varying degree.

In 34 private cases of Hector Mackenzie the disease evinced a tendency to show itself in the same family. Ricaldoni states that in one family a young man, his mother and his aunt all had exophthalmic goiter, and in another, one brother had exophthalmic goiter and the other myxedema. In a case reported by Harvier the goiter developed at 12, and the young man's mother, grandmother and an aunt on both the maternal and paternal sides had presented exophthalmic goiter. His sister had escaped the disease. The tremor in his case had been noted from early childhood. Tilmant mentions 6 instances of heredity as a predisposing factor. Souques and Lermoyez describe a family in which there have been 7 cases of exophthalmic goiter among the 16 members in 3 generations. They give illustrations of the 4 members they have personally examined. The tendency seems to be transmitted by the males. They cite a few similar familial cases on record. In one, dating from 1884, 11 of the 16 members of the family had developed exophthalmic goiter. Lenz describes several families, following one for eight generations, in which there seems to be some evidence of hereditary tendency to Graves' disease. In Climenko's patients, the mother, two daughters, and children of each of these, a boy in one case and a girl in the other, presented the disease. The transmission was a direct one and along the female line. He emphasizes that the occurrence of exophthalmic goiter in a boy aged 10 and in a girl aged 6, is in itself an extremely rare condition.

In my own experience there have been numerous instances of Graves' disease in two or more members of the same family. Also, I have observed quite a few subjects of Graves' disease whose family history presented instances of simple goiter, diabetes mellitus, and bronchial asthma.

Age.—Though usually seen during the periods of greatest sexual or active adult life, Graves' disease is observed in almost all ages. Welt-Kakek reports the case of a boy 14 years of age who showed striking signs and symptoms of exophthalmic goiter, and in whom there was a history of emotional shock. The case was of special interest because the condition is a rare one in young boys of this age. Fernandez-Sanz reports the case of a female of 82 who suddenly exhibited a most acute Graves' syndrome. The patient was entirely cured by medical treatment. Buford reports a case of exophthalmic goiter in a girl of 6 in whom, incidentally, the removal of badly diseased tonsils yielded no relief of the syndrome. In Sattler's compilation of 3477 cases, 184 occurred in patients under fifteen. In 1912, White reported a case of *congenital* Graves' disease. In 1914, Klaus reported a case in an infant 9 months old. In my own series of over 2000 cases of exophthalmic goiter seen in private and consultation practice, 43 patients were under fifteen. Of these, 22 were past 14, 16 were between 12 and 13 years old, 2 were just 10, 1 was 9½, 1 not quite 8, and 1 was just past her fifth birthday. With regard to the other extreme, I mention in the chapter on case

histories the recovery of a woman of 75, who at this writing is 78 and in good health. I have several other patients varying in age from 55 to 65 undergoing active treatment for this affection. No age is really immune to exophthalmic goiter, though, as stated, the extremes of age suffer least from this affection—the old more often than the very young.

Sex.—Probably the greater complexity and the more active sexual changes and finer adjustment of emotional structure explain why females are more prone to Graves' disease. It has been stated by some observers that the true syndrome can only exist in the female because "she has ovaries." I believe this is an overdrawn view, since the man, possessing testicles, is also apt to become involved in the symptom complex. That the sexual organs and instinct, male and female, play an important etiological rôle is manifest to all who have observed and studied this class of individuals. Since in the female the sexual variations and epochs are more marked, this sex is most susceptible to the disease. The changes in the endocrines and the autonomic nervous system incident to puberty, menstruation, childbearing, parturition, lactation, and menopause, each and all are capable of influencing the individual's susceptibility to the disease. In my experience, males constitute more than 25 percent. of patients, and in this sex the course is apt to be more severe and the prognosis graver. This is probably due to the difficulty of eradicating some ingrained harmful personal habits, and also to the sense of responsibility as a wage earner with consequent difficulty in acquiring a sense of ease—an essential asset during treatment.

Race.—Caucasians, because they lead in mental activities and strife characterizing the march of civilization, are most prone to Graves' disease. The high strung temperament of the Hebrews renders them especially prone to the disease. Mongolians are next in order in racial susceptibility. The negroes, rather prone to simple goiter, are relatively immune to Graves' disease, probably because of their phlegmatic temperament. In my observations I have seen but three negro subjects, all females. Redfern of St. Louis states that in the outpatient department of the Barnes Hospital, of the 29,000 negroes examined, 9 were



FIG. 64.—Exophthalmic goiter in a negress.

cases of exophthalmic goiter.

Geographical Distribution.—Dock observes that endemic goiter districts are relatively free from exophthalmic goiter, but alleges that this is not true of Switzerland and France, or of the region of the Great

Lakes of North America. He believes that the incidence of exophthalmic goiter is higher in England and on sea coasts than in some continental localities, but is very high in the interior of North America. Campbell, of the Medical Investigation Department of Guys' Hospital in London, asserts that in England exophthalmic goiter is more common in the country than in the towns, more common in the West than in the East, and more common on the sea coast than inland. It does not appear, to Campbell, to be specially prevalent in areas in which goiter is endemic. I, too, have observed that Graves' disease is least prevalent in regions of endemic goiter. In other words, Graves' disease is most common near the sea shore, where endemic goiter is rare, and contrariwise Graves' disease is least common in the inland districts where endemic goiter is common. Though simple goiter is endemic in many parts of the world by virtue of certain geographical conditions, such is not the case with exophthalmic goiter or Graves' disease. Of course, an endemic goiter may take on toxic symptoms and present a picture of toxic adenoma, but true Graves' disease is not endemic anywhere. It might be stated that in regions of the world where life's activities and struggles characterizing civilization are at their highest point, exophthalmic goiter is most common. This, of course, is due to man-made, not geographical conditions.

THEORIES OF THE PATHOGENESIS OF GRAVES' DISEASE

If treated in detail, the subject of the various theories advanced to explain the cause of exophthalmic goiter would entail the writing of many chapters on mere speculation. We are therefore obliged to abbreviate, and for practical purposes, we shall mention briefly the most prominent theories:

Graves regards exophthalmic goiter as a dyscrasia of scrofulous and circulatory origin.

Basedow believes it is to be a general dyserasie malady.

Marsh, Pral, and Heusinger regard the disease as a malady of the heart.

Friedreich believes that the disease is caused by an enlargement in the caliber of the coronary arteries of the heart, and this, resulting in tachycardia, would lead to the nervous phenomena.

Eulenberg, Panas, and others believe the disease to be a neurosis of central origin.

Stokes considers the affection as one of cardiac neurosis.

The **Bulbar Theory** assumes that Graves' disease is due to certain pathologic processes in the medulla or other portions of the central nervous system. Tedeschi, Warburton, and Filehne, by making section of the restiform bodies, produced a syndrome of symptoms including an increased vascularity of the thyroid, tachycardia and exophthalmos. The syndrome did not occur, however, if the section was preceded or

accompanied by thyroidectomy. Thus they concluded that Graves' disease is of bulbar origin. Sattler, too, is a supporter of this theory.

The Intoxication Theory is based upon known physiological observations upon the thyroid as a detoxicating organ, and on the fact that quite a few instances of amelioration of the Graves' syndrome have been seen to follow the removal of an infectious focus situated in the teeth, tonsils, intestines, and elsewhere. According to this hypothesis, toxins, bacterial or otherwise, by making undue demands upon the thyroid, render this organ incapable of performing fully its immunizing functions, hence the development of hyperplasia and the syndrome of Graves' disease. This theory is supported by McCarrison, Gaylor, Epstein, Thompson, and many others, and is seemingly confirmed by the experimental evidence of Halsted and Hertoghe, and the clinical evidence of many observers. In support of this view, it is suggested by Blum that albuminoid toxins are rendered innocuous by the iodization of thyroid activity, and that an undue quantity of these poisons existing in the intestines would demand a compensatory increase in thyroid activity, hence, thyroid hyperplasia. Harries suggests that exophthalmic goiter is due to excessive absorption of tryptophan from the intestine; this in turn is traceable to absence of the indol producers from the gut. In exophthalmic goiter the early disappearance of indican from the urine is of serious prognostic importance, indicating the absence of indol producers from the intestine.

Mayo, too, is of the opinion that the cell changes in the thyroid are due to increase of biochemical products by bacteria, coming from different parts of the body and acting on the organ. Gastro-intestinal intoxication as a cause of Graves' disease is emphasized by McCarrison and more especially by Lane. This last observer reports the case of a girl 19½ years of age, who suffered with Graves' disease of 18 months' duration. Operation was performed, in which a gastrojejunostomy and an appendectomy with the removal of intestinal kinks and adhesions resulted in cure of the patient within a few months.

Focal infections, though regarded by many as the most important of exciting causes of Graves' disease, are in my experience more often coincidental than causal in the majority of instances. Though I firmly believe that focal infections should receive proper attention, whether in tonsils, teeth, nasal sinuses, gastro-intestinal or genito-urinary tract, the percentage of patients actually cured by tonsillectomy, removal of teeth, and other foci, is remarkably small. In many instances, however, judging from the frequency with which diseased teeth and tonsils are present in Graves' disease, and the infrequency with which improvement in the syndrome occurs following the eradication of the foci, it seems reasonable to infer that an infectious focus, once having incited the syndrome, its removal has little influence upon the already existing symptomatology. That a causal relationship has been assigned to a mere coincidence is

obviously the case in many patients. It must be insisted upon, however, that irrespective of their etiological importance, focal infections require prompt attention.

General infections, also, may serve as exciting factors of Graves' disease. Rheumatism, tuberculosis, syphilis, and less often, pneumonia, typhoid, and other general infections fall into this category. Knopf often meets with young girls suffering with both Graves' disease and pulmonary tuberculosis. Bialokur finds that in 10 percent. of his tuberculous patients there are symptoms of exophthalmic goiter, predominantly seen in women (1 man to 10 women). He is of the opinion that Graves' disease may indicate the existence of a latent tubercular infection, and that successful treatment of the former may improve the latter disease.

Engel-Reimers states that swelling of the thyroid occurs in 50 percent. of early cases of secondary syphilis. Late secondary and tertiary manifestations of syphilis of the thyroid are uncommon and respond readily to specific treatment. Smit records two cases of toxic thyroiditis due to syphilis with all the symptoms of Graves' disease, in women aged respectively 34 and 52 years, who were both cured by antisyphilitic treatment. Hardey observes the presence of syphilis in 55 percent. of cases of Basedow's disease, and tuberculosis in 18 percent. These, in my opinion, are rather high figures.

Roeder reports 8 cases of toxic goiter (3 adenomata and 5 hyperplastic) following immediately on an attack of epidemic influenza. Todd observed 16 cases of Graves' disease in a group of 1500 cases of influenza; the signs and symptoms first appeared at times varying from the sixth to the twenty-first day of the illness, and in all but one fatal case, they developed during convalescence.

Drugs, especially iodin and thyroid extract, may serve as exciting causes of Graves' disease in *susceptible* persons. I do not mean to imply that these substances are capable of producing Graves' disease universally. Predisposition to Graves' disease is the essential requirement. Under these circumstances iodin or thyroid extract may serve the same function etiologically as psychic trauma,—the torch inducing the conflagration in an inflammable subject. In Hollervorden's experience the administration of iodin was beyond question the onset of the acute phase of exophthalmic goiter in no less than 25 cases out of 100. This, it appears to me, seems rather a large percentage due to this cause.

I have had several instances of Graves' disease under my care the onset of which began shortly after the use of thyroid tablets taken presumably for the purpose of overcoming an already existing slight hyperplasia of the thyroid. It required but 10 to 30 grains in each instance to bring on a frankly outspoken Graves' syndrome, with all its dramatic manifestations.

The Kinetic Theory of Crile is based upon the view that exophthal-

mic goiter is due to an affection of the "kinetic system," *i.e.*, the brain and muscles, together with the suprarenals, liver and thyroid. Thyroid hyperplasia is a result, not the cause of Graves' disease; the latter is due to physical injury, heat and cold, emotional and sexual disturbances, infections, autointoxication, and other causes. These bring about the syndrome through activating the kinetic system.

The Thyroid Insufficiency Theory was advanced by Gauthier in 1885 and has many followers. In this hypothesis it is claimed that myxedema and exophthalmic goiter are due to the same cause—insufficient thyroid functioning. The former is the result of defective utilization of the iodin assimilated from the food and metabolized in the liver or elsewhere. Exophthalmic goiter, on the other hand, is the result of injury from iodin getting into the blood and insufficiently metabolized. This assumption explains the coincidence of myxedema and exophthalmic goiter, which is frequently observed and which it is impossible to explain by the current theory that myxedema is the result of hypothyroidism, and Basedow's disease of hyperthyroidism. As he remarks, a glass cannot be full and empty at the same time. The reasoning of those supporting the dysthyroidism theory possesses many points in common with the above tenets.

The Psychic or Emotional (Neurogenic) Theory.—Oswald emphasizes the fact that a predisposition to this disease is necessary, and the genetic factor lies in the nervous system. Mental strain, continuous excitement and the like are exciting causes. The primary cause is a weakened nervous system, and the struma is a secondary symptom. The thyroid receives its impulse from the nervous system of which it is physiologically a part and acts through a specific substance as an intensifier. Says Mackenzie: "Fright, intense grief, and other profound emotional disturbances have been recognized as causes of this pathological condition, but I do not think that sufficient attention has been paid to the very close connection between the chronic symptoms of Graves' disease and the more immediate effects of terror. The description given by Darwin and Sir Charles Bell of the condition of man in intense fear might almost have been written with regard to a sufferer from this disease. The heart beats quickly and violently so that it palpitates or knocks against the ribs. There is a trembling of all muscles of the body. The eyes start forward, and the uncovered and protruding eyeballs are fixed on the object of terror. The surface breaks out into a cold, clammy sweat. The intestines are affected. The skin of the face is flushed, down over the neck to the clavicles. . . . Of all the emotions, fear is the most apt to induce trembling. There are one or two of the minor symptoms of Graves' disease whose independent occurrence is well known. These are the pigmentary changes in the skin and hair, the falling out of the hair and epistaxis.

"Such being the condition resulting from severe terror, we have only

to imagine the condition to become prolonged by a failure of the nervous system to recover its balance and right itself, and we have a more or less complete clinical picture of Graves' disease. . . . It is likely that the alteration of the function of the thyroid body, whose importance in connection with the nutrition and the transmission of nerve force has been amply demonstrated, has a good deal to do with many of the secondary symptoms to which I have called attention, but the real disease is a widely distributed derangement of the emotional nervous system."

In this connection it may be remarked that soldiers under unaccustomed physical and emotional strain are particularly susceptible to thyroid hyperactivity. The recent World War has engendered thousands of such instances, many of which have been erroneously termed "shell shock." These men are exceedingly nervous, lose weight rapidly, and many complain of distressing palpitation and insomnia. Hysteria, melancholia, hallucinations and the manias are common. On examination, the thyroids of most of these men are palpably increased in size, and though the number of cases of exophthalmos is small, tachycardia, arrhythmia and vasomotor instability are very common. Johnson made observations on 50 soldiers who left the firing line complaining of weakness, uncontrollable nervousness, throbbing headaches, dizziness, palpitation, and precordial pains, more especially on exertion. Occasionally digestive discomfort and diarrhea or frequency of micturition were complained of. Sleep was irregular and easily disturbed. Dreams, in which they would wake up in a profuse perspiration, were common. On examination, these patients appeared pale, looked ill and were exhausted. The mental state was one of subdued excitement. More or less prominence of the eyes was exhibited by all the cases. Tremor was a constant phenomenon. Other signs of hyperthyroidism were also generally present. Marañon also reports a considerable number of cases of exophthalmic goiter occurring in consequence of stressful circumstances during the war. Hoxie reports that soldiers came back to the base hospital after exhausting battles, with exposure to gas and infectious disease, showing a low blood pressure, dilated heart, and similar signs of exhaustion. The blood pressure would gradually rise until it reached 160 mm. With this increase in pressure was urinary urgency, tremor, heightened reflexes, and an increase in the size of the thyroid. In other words, in this stage the men presented the picture of Graves' disease.

I have observed shock of operation anywhere in the body to be followed by typical evidences of the syndrome of Graves' disease in susceptible individuals.

The Toxic-Neurogenic Theory of Sajous.—It is always of interest to quote the views of Charles E. de M. Sajous, a pioneer in endocrine research. In an address before the American Therapeutic Society in

1919, he said in part: "There have long been . . . two main theories regarding exophthalmic goiter, first, that it is due to excessive thyroid activity; second, that it is a nervous disorder. Time has shown, however, that, as is often the case with strong and well-sustained hypotheses, both were correct and more or less interwoven. Moreover, other ductless glands have been found to participate in the morbid process, the adrenals and thymus in particular. . . . We now know that various toxins originating from the intestines, pyogenic disorders of the tonsils, nasal and the faucial cavities, peridental and gingival pyorrhea, gastrop-tosis, with prolonged retention of ingesta, etc.—may underlie the morbid process. These various sources of general intoxication obviously constitute the fundamental factor of the disease and yet, most writers, particularly those who speak of 'symptomatic' treatment, fail to refer to them. The reason is not far to seek: Some overlook the toxemia. Others, though admitting it, fail to take into account the one factor which elucidates the whole morbid process, viz., that it is in defending the body against intoxication that the thyroid body becomes abnormally active. . . . Briefly, fright, anger, etc., bring about disintegration of the nerve cell, by subjecting it to violent stimulation, which means excessive metabolic activity. And it is here that the primary toxemia or cause of exophthalmic goiter in these cases appears, e.g., excessive metabolism of the nerve cell is known to produce phosphoric acid, cholin, and also a substance known to be particularly poisonous, *neurin*, a body closely allied to muscarin, especially. So sensitive is the thyroid gland to the latter poison, in fact, that it was once believed that the one function of the organ was to destroy neurin as fast as formed. In the light of these facts, therefore, we again realize that a poison, though neurogenic this time, can become the primary cause of the disease. But why, the excessive stress due to fear, rage, etc., once terminated and entirely appeased, does the morbid process continue? Why do all the morbid symptoms, particularly those of nervous origin, persist? This is due to a vicious circle. The thyroid, powerfully stimulated to react against the intoxication, itself becomes a destroyer of the nerve cell. This becomes intelligible when we recall that besides chromatin, the nerve cell is likewise rich in fatty substances, lecithin (containing stearic, palmitic, or oleic acid) in particular. If we now recall the familiar fact that thyroid gland first attacks fats, breaking them down sooner than any other tissues, we can realize why it is that excessive thyroid activity so actively disturbs the nervous system. Briefly, *a severe mental stress—fear, rage, deep grief, etc.,—causes excessive catabolism in the nerve cells, and the excretion by them of high'y toxic wastes, including neurin; these poisons by provoking a defensive reaction of the thyroid, cause it to break down fats, including the fatty components of the nerve-cells, thus establishing a vicious circle, by perpetuating the catabolism of these cells and the formation of poisons.*"

Sympathetic Theory.—The theory that the cervical sympathetic ganglia are responsible for exophthalmic goiter is one of the oldest. Koeben, Aran, Troussseau and Charcot were among the first to describe it. Claude Bernard's experiments on the sympathetic and vasomotor nerves were largely responsible for this theory taking a strong foothold in the minds of observers. Then followed the observations of Graefe, Charcot, Aran and Troussseau. This latter observer, according to Roussy, declared, after an autopsy revealing a diseased inferior cervical ganglion: "The functional symptoms of Graves' disease originate from the passive congestion of the great sympathetic, or perhaps, from a persisting structural lesion of the ganglia of this system."

That any agency causing continuous excitation of the sympathetic nervous system may give rise to a syndrome closely resembling that of Graves' disease has been proved by competent observers. Cannon, in 1916, fused in six cats the anterior root of the right phrenic nerve with the right cervical sympathetic strand. This increased the pulse rate, and the basal metabolism (100 percent.), caused diarrhea, and made them excitable. In two that died of the disease, the cortex of the adrenals was greatly enlarged.

Wilson found the goat to be an exceptionally favorable animal for the study of thyroid problems on account of the close resemblance of the gland to that of man. Studies were made in 19 cases. The superior cervical sympathetic ganglia were exposed and stimulated either electrically or by injections of various sorts of bacteria. It appeared that irritation of the ganglia may produce histological pictures in the ganglia themselves and in the thyroid, which parallel those found in various stages of progressive and retrogressive exophthalmic goiter. This evidence supports the suggestion which Wilson has previously offered that exophthalmic goiter is due to overstimulation of the thyroid gland through the nerve supply, and as a result, usually, of a local infection in the cervical sympathetic ganglia.

The sympathetic theory is variously explained by different authors. Koeben, in 1855, expressed it very simply, stating that "the syndrome is due to compression of the nerve trunks by the thyroid tumor." The modern view is presented by Roussy, who elucidates it as follows: Excitation of the cervical sympathetic gives rise to exophthalmos and tachycardia—two of the principal signs of Basedow's disease; simultaneously with these are produced pupillary dilatation, flattening of the crystalline lens, increased intra-ocular tension, and such vasomotor phenomena as constriction of the vessels of the conjunctiva, iris, tongue, lips, cheeks, etc. In commenting upon these phenomena of cervical sympathetic irritation it must be said that dilatation of the pupils and pallor of the face are *not* evidences of Graves' disease. To produce such other manifestations as dilatation of the vessels of the neck and of the thyroid, the inverse experiment must be made, that of *section*,

bringing about paralysis of the cervical sympathetic. But when this is done, instead of exophthalmos, we produce retraction of the eyeballs. Thus, says Roussy, although excitation and paralysis of the cervical sympathetic give rise to contradictory phenomena, nevertheless the syndrome of Basedow's disease lends itself to both of these opposed clinical pictures. All the adherents of the sympathetic theory have striven to solve this problem but have not yet succeeded. "Finally," says Roussy, "we find it difficult to accept seriously the theory that the cervical sympathetic is responsible for the syndrome of exophthalmic goiter when the thyroid theory has so much in its favor. The most powerful argument against it is that it does not explain all the facts in the clinical picture. We fail to see much justification of the sympathetic operation to favor its performance. According to Jaboulay, it succeeds specially in those who have little or no goiter and are perhaps not at all affected by true Graves' disease."

Pulay asserts that Graves' disease is a form of increased irritability of the sympathetic system, but this alone does not cause Graves' disease unless the patient has also a *status degenerativus* and unless there occurs also a special stimulation of the sympathetic (psychical, traumatic, or infectious), giving rise to the beginning of the disease. He states that it is not true that the cause of the disease is abnormal functioning of the thyroid. The thyroid malfunction is rather a result of augmented sympathetic activity, as are the many other Graves' symptoms. No value is attached to theories ascribing a primary etiological rôle to the thymus or pancreas in this disease.

Barker reminds us that symptoms of sympathetic irritation may be produced by amines of putrefactive decomposition of proteins or amino-acids through bacterial action, the most common source of which is the gastro-intestinal tract.

Thymus Theory.—Hart, Garré, Capelle, Bayer, Sinorzerksy, Bircher, Basch, Matti, Gudernatsch, and others are inclined to believe that the thymus gland is largely, if not wholly, responsible for the Graves' syndrome. It is even asserted by some observers that there is a pure thymogenic form of the disease. Nordman thinks that whenever the thymus is enlarged, hyperactivity of the thyroid is apt to occur. Adler, too, believes that the thymus is responsible. His experiments on frogs prove that the cause of Graves' disease is never an abnormal function of the thyroid. The goiter is caused by Graves' disease, and not, as many investigators believe, *vice versa*. When pregnant guinea pigs are fed with large doses of thymus, they abort. When the animals are killed after this abortion, one finds hemorrhage in the adrenals. When smaller doses of thymus are given, the development of the embryo, according to Adler, proceeds much faster than normal, and perfectly normal young animals are born much earlier than in the controls. Halsted finds from the postmortem examination of cases of exophthalmic

goiter that have died of intercurrent disease that the thymus gland is persistent in about 82 percent., and in most cases that have died of heart failure after operation, enlargement has been found in about 95 percent. From facts gleaned at the autopsy table, from experiments on animals, and above all, from the results following primary thymectomies, Halsted has convincing evidence that the thymus gland may play an important part in exophthalmic goiter, and in some cases assume the title rôle.

On the other hand, seemingly negative deductions are not lacking. In an attempt to determine whether an excess of the product of thymus activity in the circulating blood could cause exophthalmic goiter, experiments were made by Eddy on rabbits. Two rabbits served as a control. Three rabbits were given hypodermic injections of thymus substance in the proportion of 5 mg. per kilogram of body weight, and three in the proportion of 10 mg. per kilogram. Forty injections were given to each rabbit. There was no evidence of the production of symptoms characteristic of exophthalmic goiter by the thymus gland substance employed in either group of rabbits. These experiences are confirmed by those of Gebele whose results were negative even though the transplanted thymus was of Basedowian origin.

Blackford and Frelich, of the Mayo Clinic, in a study of 100 necropsies of fatal cases of exophthalmic goiter, conclude that a hypertrophic thymus is present in all exophthalmic goiter patients under 40 years of age, and in half of those over 40 years of age. "Hypertrophy of the thymus is inversely proportional to the age of the patient and directly proportional to the duration of the disease. . . . Our records, in general, show that the most severe acute cardiac damage is seen in those violent intoxications in which the onset occurs after the age of 40; that is, in the 'menopause' group. These as a rule have a small thymus or no thymus. In every case of cardiac damage in which a thymus was found, there was definite parenchymatous hypertrophy in the thyroid with no demonstrable thymus. . . . The findings indicate that a thymus hypertrophy and lymphatic hyperplasia should be considered as a result rather than as a cause of the intoxication in hyperplastic or nonhyperplastic goiter. Hypertrophy of the thymus probably depends on the presence of vestigeal tissue at the onset of the disease which may regenerate under toxic stimulation."

Crile, in a paper written in 1921, states that he has never had a single case of this disease in which he had reason to believe an enlarged thymus to be a complicating factor.

It seems plausible to assume that the enlargement of the thymus (as indeed the enlargement of the remaining lymphatic glands) is caused by and is therefore *secondary* to the surcharging of the blood with the toxins of the disease. In support of this hypothesis we have only to recall that the lymphatic tissues of the body usually assume the rôle of filters

for the protection of the blood stream against toxins, and may undergo a compensatory hypertrophy in the performance of this protective function.

The Adrenal Theory.—Some observers hold that a deranged structure and function of the suprarenal glands is responsible for Graves' disease. In support of this view it is pointed out that areas of pigmentation may constitute a prominent element in the symptomatology. Moreover, it has been observed that symptoms of Addison's disease occasionally precede, coexist with, or follow those of the syndrome of Graves' disease.

Here the statements of Cannon are suggestive: "The bodily changes accompanying strong emotions, such as fear and rage, are related to certain glands of internal secretion, especially the adrenals, and probably the thyroid. When infuriated, a cat's pupils are dilated, hair stands erect, heart is accelerated, the activities of stomach and intestines inhibited, and muscular fatigue lessened. There is an increased liberation of sugar from the liver, an increase of circulating erythrocytes, and the coagulation time of the blood is decreased. These changes may also occur in man. Fear and rage are emotions underlying the struggle for existence and the changes noted increase the efficacy of the organism for physical struggle. Most of the phenomena noted are due to increased circulating adrenin, the adrenal glands being stimulated by the sympathetic nervous system." This author believes that the reason organs disturbed during emotional stress are not disturbed at other times is that a high neuron threshold is interposed between the central nervous system and the visceral cells. This threshold is only lowered from great emotional experiences, and there is a frequent disturbance of these organs, causing dyspnea, tachycardia, and glycosuria. Besides a routine function, the adrenals have an emergency function in times of great excitement. This is likewise true of the thyroid, its increased activity augmenting the metabolic processes and aiding the efficiency of the adrenin.

Crile believes that exophthalmic goiter is not due to thyroid changes alone but also to altered function of the suprarenals. "From the clinical data in certain cases of exophthalmic goiter in which resection of the thyroid was followed by an increased nervous stability and increased body weight, while there remained a flushed face, sweating, and an increase of the frequency and force of the heart beat, we may infer that while the thyroid symptoms of the disease were relieved, the suprarenal group persisted. It may be that the excision of part of the suprarenal tissues will supply the complete cure for such cases as these."

Swieicki, of Posen, is also inclined to regard Graves' disease as due to hyperactivity of the suprarenals; the vasomotor and secretory symptoms, including tachycardia, tremor, and exophthalmos, being caused by an increase of secreted adrenalin.

Friedman is another observer who believes that much of the symptomatology of Graves' disease is due to adrenal disturbance. Strong supporters of the adrenal theory point out that (a) hyperactivity of the adrenal medulla is evidenced by tremors, alimentary glycosuria, occasional hypertension, and possibly exophthalmos; (b) hypo-activity of the adrenal cortex is evidenced by uric acid retention, hyperpigmentation, loss in weight, asthenia, and gastro-intestinal disturbances.

Marine and Baumann have recently shown that removing or crippling (by freezing) the suprarenal glands in rabbits causes a disturbance in metabolism, usually characterized by increased heat production and carbon dioxid output. This disturbance appears definitely related to the completeness of removal of the cortical function. The experimenters add, further, that there are many points of similarity between the syndrome that results from such suprarenal injury in rabbits and exophthalmic goiter in man. Marine believes that the pendulum is again swinging toward the polyglandular hypothesis. "My own conception of the fundamental lesion in exophthalmic goiter," states he, "is that of an exhaustion insufficiency of the adrenal system."

In view of the occasional evidences of a combination of Addison's disease and exophthalmic goiter in the same patient, and in consideration of certain significant clinical and experimental phenomena and the fact that the administration of suprarenal extract is of signal benefit in a certain percentage of Basedow patients, the conclusion that the suprarenals play *some rôle* in the syndrome of Graves' disease seems justifiable.

The Parathyroid Theory.—The incrimination of the parathyroids as the causal agent in the production of exophthalmic goiter is suggested by the remarks of Gley. This observer bases his views especially on the statement that the parathyroid tissues are almost identical with those of the thyroid, the former being an undeveloped or embryonic form of the latter, and that the tremor and many other symptoms indicate a primary parathyroid derangement. Though this theory found favor in the eyes of Jean Clunet and others, the vast majority of observers do not accept it seriously.

The Pituitary Theory.—In 1905, and again in 1911, Salmon pointed out that the Basedowian syndrome is produced by a derangement of function of the pituitary. He bases his deductions upon the following points: 1. Experimental thyroideectomy has, in a large number of cases, produced a hypertrophy of the pituitary, characterized microscopically by a picture of hyperfunctioning glandular cells (Lucien, Parisot and Thaon, Larson). 2. Pituitary extract exerts a vasoconstricting action on the thyroid, which is quite intense and durable. 3. There exist in literature several observations of syndromes of acromegaly associated with Graves' disease, some of which were verified at autopsy by the discovery of hypertrophy or neoplasm of the

pituitary. 4. Pituitary ootherapy has ameliorated a number of cases of Basedow's disease.

That Salmon's theory is more than mere speculation is exemplified by the statements made in the chapters on Physiology and Treatment. Hypertrophy or disease of the pituitary body is commonly seen in autopsies of cases of Graves' disease; moreover, there is accumulating evidence to convince one of the value of pituitary extract in this disease.

The Gonad Theory.—It is obvious that in many instances of Graves' disease the organs of reproduction, especially in the female, are etiologically involved. The relation of the sexual apparatus to the thyroid and other endocrines has been elucidated in the chapter on the physiology of the thyroid. There is strong evidence to the effect that the thyroid and ovarian secretions neutralize each other. Moreover, it is observed that Graves' disease may appear during the changes of puberty, pregnancy, the menopause, and after hysterectomy. The frequency with which the correction of pelvic disease associated with exophthalmic goiter causes an amelioration of the syndrome seems to confirm the gonadal theory. Thompson, after reviewing the relations of the thyroid to menstruation and pregnancy, reports three cases suggesting to him that the hyperplasia and cell proliferation of the uterus found in fibromyomas may activate the thyroid, and that the myocardial weakness so often found with fibromyomas may be due to hyperthyroidism and not directly to the tumor. Delestre asserts that lesions of the genital system occur in 96 percent of patients with exophthalmic goiter. Ovarian insufficiency is the most prominent feature; genital disturbances usually precede the other evidences of the syndrome, and are not the result of the disease. Delestre reports a case of the disease in which the removal of a suppurating ovarian cyst caused considerable improvement of the general condition after thyroidectomy had produced no result. Again, many reports are available indicating good results from ovarian ootherapy in exophthalmic goiter.

The Hyperthyroidism Theory assumes that Graves' disease is due to thyroid hypersecretion. The adherents of this theory offer the following arguments in its support: (1) The condition is the direct antithesis of myxedema, in which there is a lack of thyroid substance in the blood. (2) Partial resection of the goiter or partial ligation of the blood supply causes a diminution of the symptoms. (3) Most, if not all the symptoms of exophthalmic goiter may be artificially produced by the oral administration of thyroid. (4) Thyroid gland, administered to a subject of Graves' disease, aggravates the symptoms. (5) Other theories fail to explain satisfactorily the causation of the syndrome.

Moebius and Renaut are among the earliest proponents of this theory, Béclère, Marie and others concurring with Moebius in stating the syndrome to be the result of a hyperthyroidization of the body. This conclusion is confirmed by Ballet and Enriquez who, in 1895, claim

to have experimentally produced the Basedow syndrome by thyroid administration. In criticism of the Moebius theory, an editorial in *Endocrinology* (Vol. II, No. 4), states: "One observation which is apparently well attested renders untenable the conception that Graves' disease is a simple hyperthyroidism. This observation is that the disease may exist simultaneously with hypothyroidism. Thyroid secretion cannot be both augmented and depressed at the same time any more than can a physical body be simultaneously up and down. Various labored explanations of the paradox have been offered, but they have the defect of leaving the contrary fact still standing. Moreover, cases in which thyroid medication has proved beneficial in Graves' disease have been repeatedly described. The blood picture—a reduction of neutrophiles, lymphocytes, and mononuclear leucocytes—is the same in both Graves' disease and myxedema. It would seem, then, that there is some element in common in the etiology of both conditions." Rogoff's experiments on tadpoles failed to indicate toxic effects from blood of thyroid veins of subjects of exophthalmic goiter, nor from animals with hyperplastic glands. Marine and Williams have shown that the hyperplastic thyroid possesses less iodin than does the normal gland, and since the toxicity of thyroid substance depends upon its iodin content, the hyperthyroidism theory appears untenable. Finally, the fact that Cunningham, Hutchinson, Gley, Marine and Williams, Kendall, Carlson, and many others have been unable to produce the typical syndrome of Graves' disease by the administration of large doses of thyroid substance to man and other vertebrates, strongly negatives the hyperthyroidism theory. Despite Notthaft's case in which 1000 thyroid tablets were ingested in 5 weeks, and several other cases of lesser severity, including a few of my own, in which thyroid ingestion was responsible for an onset of Graves' disease, it must be recalled that there are hundreds, probably thousands, of persons who have been and are now taking tablets of thyroid substance carelessly, without untoward effects or with mere evidences of artificial hyperthyroidism. It is only in those inherently predisposed to the disease that the ingestion of thyroid substance or large doses of iodin may serve as an exciting cause of the Graves' syndrome.

The Dysthyroidism Theory assumes that Graves' disease is due to an alteration in the *quality* or *nature* of the thyroid secretion. This theory is based upon the fact that many of the signs and symptoms of the disease are traceable to thyroid deficiency, and that in a considerable percentage of patients evidences of hyper- and hypothyroidism occur simultaneously. Moreover, it is occasionally reported that the Graves' syndrome is ameliorated by thyroid otopathy, and that according to Janney, Halverson, Bergeim, and Hawk, "there is an added retention, not a toxic loss, of nitrogen and other protein metabolites on thyroid administration in Graves' disease." Lampe, Liesegang, Klose, Janney, and quite a few other students of the Graves' syndrome accept

the dysfunction or dysthyroidism theory as explanatory of the etiology of this affection.

Pluriglandular Theories.—These are numerous and variable and lend themselves to considerable speculation. Stengel, Solomon Solis-Cohen and others firmly believe that the thyroid excess in the blood, through thyroid hyperfunction, is but an incident in the chain of events occurring in all the other glands, especially the endocrines of the body, all of which conspire to produce the syndrome. As observed in the chapter on Physiology and elsewhere, there are pathologic, clinical and therapeutic evidences to confirm the belief that the suprarenals, pituitary, parathyroids, ovaries, thymus, and even the pancreas and liver are interrelated in function with the thyroid, and in the event of a departure from the normal structure and function of one of these glands, the others are affected.

In a personal communication, Professor Solomon Solis-Cohen, whose wide experience as an internist stamps him as an authority on this subject, expresses the following clear-cut views, pregnant with significance: "Graves' syndrome is *one* of a number of related syndromes shading into one another (like a spectrum of which it may be considered the red, while Raynaud's syndrome is the violet) showing varying degrees of unbalance or incoordination (*ataxia*) in the vegetative (autonomic) nervous system and its endocrine appendages. This basic condition of *autonomic ataxia* is generally congenital and commonly inherited, but in rare instances appears to have been acquired. Under the incidence of various exciting causes and local determinants, varying syndromes appear in the same individual at different periods of life—in different members of the same family—in different families of the same clan. The thyroid enlargement, with or without hyperactivity and later hypoactivity, is secondary; and its results are therefore *epiphemonal* and not *fundamental*. It is an important incident, but only an incident."

Leonard Williams contends that Graves' disease is not only not a hyperthyroidism but is not a disease of the thyroid gland at all. He states that the most outstanding features of the complaint, namely, exophthalmos and cardiac troubles, are due to the implication of other glands, the exophthalmos being due to *adrenal* excess and the cardiac symptoms to enlargement of the *thymus*. He considers that this enlargement, which occurs in 85 percent. of cases, causes not only cardiac symptoms by pressure on the base of the heart and great vessels, but also many of the nervous symptoms by pressure on the vagus, sympathetic, and phrenic, as well as mental symptoms by interfering with drainage from the brain. He regards Graves' disease as due to toxemia in which all the members of the endocrine hierarchy are involved.

McCarrison, too, believes that Graves' disease is not caused by thyroid hypersecretion, but by a combination of endocrine factors disturbing

the metabolism. He rightly states that the disease is preëminently one of modern civilization, and that faulty feeding is an important etiological factor.

Roussy points out that the sympathetic is also implicated in this glandular interrelationship, in that adrenalin causes sympathetic excitation, and that the thyroid secretion excites the sympathetic and autonomic systems simultaneously.

The Vagotonia and Sympatheticotonia Theory of Eppinger and Hess, in which the sympathetic and parasympathetic systems are each to a variable degree responsible for the signs and symptoms of Graves' disease, is an attractive hypothesis and is mentioned in the chapter on Symptomatology. Recent observers, however, are less prone to regard this theory seriously.

Related to the above theory is that recently proposed by Kessel, Lieb and Hyman, in which it is claimed that the syndrome of "autonomic imbalance" precedes that of exophthalmic goiter and that the only difference between the two syndromes is the presence in the latter of an increased basal metabolism. These authors state that patients with autonomic imbalance present a typical picture of Graves' disease, with or without goiter. They find that the manifestations of these patients are clinically divisible into three groups: (1) The registration in consciousness of somatic activities which normally proceed unconsciously, as palpitation; (2) objective functional disorders in organs which themselves were apparently healthy (tachycardia, diarrhea); (3) symptoms of obscure origin which were accentuated by the administration of adrenalin (tremor, asthenia). With the possible exception of thyroid enlargement, all of these symptoms and signs were *sympathomimetic*. This term was adopted from Barger and Dale to denote manifestations that are tantamount to electrical stimulation of the thoraco-lumbar division of the involuntary nervous system, or to stimulation of the same system by adrenalin. That "disturbance in the involuntary nervous system" plays an important rôle in the causation of exophthalmic goiter cannot be refuted, and the statement that "goiter is probably not responsible for the autonomic imbalance," and to be regarded "as a purely secondary and symptomatic feature of exophthalmic goiter" is entirely in accord with my own observations. But the statement that "the other ductless glands play no evident rôle" can scarcely be accepted in the light of existing knowledge of the disease. Autonomic imbalance can hardly exist without endocrine imbalance, and *vice versa*, so that we must finally conclude that we are dealing with a *neuro-endocrine* imbalance.

Having reviewed a few of the great number of theories advanced to explain the causation of Graves' disease, we find ourselves at a loss to form a concrete notion of the pathogenesis of this affection. What we require is a working basis practical enough to be employed when con-

fronted with these unfortunate sufferers. Such a conception of the etiology is highly important in this work, since without it we must flounder about in our history taking and in the search for etiological factors in the case before us. A theory of the pathogenesis of Graves' disease which has served me satisfactorily for many years and which has enabled me to make a satisfactory historical investigation of all my patients, with consequent facilitation of therapeutic approach, is what I term

The Neuro-Endocrine Theory.—This is not a novel hypothesis, but a combination or merging of the most plausible of the previously mentioned theories, the *neurogenic* and *pluriglandular* theories, based upon my view that these two theories are necessarily interdependent, and that *Graves' disease is a generalized dysfunction of the vegetative nervous system and of the entire chain of endocrine organs—a neuro-endocrine dysfunction.* This conception of the disease is substantiated by physiological, pathological, clinical and therapeutic facts amply presented in this book. According to this theory the patient has an inherited, rarely an acquired neuro-endocrinopathy, serving as the predisposing factor, and it requires but the torch of an exciting cause, usually an emotional strain, a psychic trauma or an intoxication, to bring on the conflagration of the syndrome.

There are many things yet to be learned about Graves' disease, and many more things which are now regarded as facts will probably be regarded as fallacies in the course of time. But those of us who study these patients in large numbers from an internist's point of view cannot escape the conclusion that the causal factors of Graves' disease are really more widespread than was dreamed of some years ago.

We know that (1) hereditary influences play an important part in susceptibility to the disease, as evidenced among other things by the frequently observed multiplicity of cases and allied conditions in the same family; (2) that this hereditary predisposition may become intensified by acquired factors through errors in the conduct of life or through maladaptation to the world at large; and (3) that in nearly every case of Graves' disease there is superimposed upon predisposition an exciting factor accounting for the onset of the syndrome. According to the neuro-endocrine theory, we might tabulate the etiology of Graves' disease as follows:

A. Inherited predisposing factors:¹

1. Autonomic imbalance.
2. Endocrine imbalance.
3. Reduction of threshold of nervous and emotional reaction.
4. Vasomotor ataxia.

¹ The inherited predisposing factors are interrelated and inseparable.

B. Acquired predisposing factors:

1. During infancy:
 - (a) Faulty hygiene, diet and discipline;
 - (b) Accidents, as falls, burns, fright, etc.
2. During childhood:
 - (a) As in infancy;
 - (b) Faulty school life; impressions from companions, teachers; over-ambition;
 - (c) Unhealthy influences of home life; table talk, parental behavior, and other home circumstances;
 - (d) Improper recreation: movies, theaters, reading, etc.
3. During puberty and adolescence:
 - (a) Faulty school life as in childhood;
 - (b) Faulty impressions from home environments, relatives, companions;
 - (c) Improper recreations: movies, theaters, dancing, reading, etc.;
 - (d) Inappropriate preparation for adult tasks of life;
 - (e) Harmful dietetic and hygienic habits;
 - (f) Changes incident to growth and development:
 - i. Physical—thyro-gonadal hyperplasia, menstruation;
 - ii. Instability of mental activity and aberrant assertion of sexual instincts.
4. During adult life:
 - (a) Faulty dietary habits;
 - (b) Harmful occupational, business, or professional factors; over-activity or inactivity;
 - (c) Improper sleep—quality, quantity, and regularity;
 - (d) Errors in social and sexual life;
 - (e) Faulty mental habits—pessimism, worriment, etc.;
 - (f) Errors in quality and quantity of recreation.

C. Exciting causes:

1. Mental—psychic trauma (either acute or sustained):
 - (a) Occupational—occupations entailing extreme nervous strain, e.g., school teaching, telephone operating; those entailing duties at variance with the desires of the individual, resulting in continuous distress;
 - (b) Economical—maladjustment between income and expenditure, extravagant habits, bankruptcy, etc.;
 - (c) Social—“high life” and its ambitions; discord with relatives and friends; misplaced love; hatred, jealousy, and other passions;
 - (d) Sexual:
 - i. Men—sexual neurasthenia, impotence, priapism, etc.;
 - ii. Women—vaginismus, sterility, sexual incompatibility, frequent pregnancies;
 - (e) Intense emotional strain—sorrow, anger, chagrin, distress, prolonged engagements;
 - (f) Accidents—acute fright, shock, etc., with or without physical injury.
2. Physical:
 - (a) Focal infections in tonsils, sinuses, teeth, gastrointestinal and genitourinary tract, etc.;
 - (b) General or systemic infections, especially tuberculosis, syphilis, and rheumatic fever;

- (c) Autointoxications—intestinal, renal, biliary;
- (d) Neoplasms, especially pelvic;
- (e) Occupational—extreme physical exertion, hazardous occupations associated with danger to life and limb, exposure to extremes of temperature and to poisons;
- (f) Accidents—railroad, automobile, conflagrations, earthquake, etc.;
- (g) Ingestion of large doses of iodin or of thyroid extract.

Of the precise nature of inherited influences we are still uncertain. The fact is, however, that subjects of Graves' disease are nearly always spoken of by their parents as having been nervous and delicate during infancy; that childhood was replete with persistent nervousness and semi-emotional outbreaks. School work was never a task mentally, though evidently physically fatiguing. Precocity of mind at the expense of physical vitality is frequently described as characterizing school life, though most often these subjects present a floridity of the skin, indicating apparent good health.

Evidences of Predisposition to Graves' Disease.—So far as I am able to determine in my experience with a large series of subjects of this sort, the earmarks characterizing a young adult possessed of susceptibility to Graves' disease are the following: (1) There is *heightened cerebration*. Irrespective of the amount of schooling obtained, the ambitions and mental alertness of these persons are beyond those of the average individual of similar station in life. There is frequently a fondness for classical music, a surprising appreciation of the other esthetic arts, a desire for psychological pursuits and adventures into the realms of the occult, a craving for literature and lectures apparently beyond the mental reach of the subject; in the professions, an aptitude to reach ahead of contemporaries; in business, ambitions worthy of a captain of industry. It is from this class of individuals that many of the talented persons and geniuses arise, if the mental activities are well applied; if not, such a person may become an incipient or an actual case of dementia praecox. Occasionally the mental status is somewhat uncertain; conversation upon a topic, though intense and earnest is unsustained, interest flitting from one subject to another with irrelevant sequence and frequency, bespeaking a veritable frenzy to acquire an encyclopædia of information within a brief while,—an ambition never satisfied, burning away the energies day after day, to say nothing of the nocturnal activities of the subconscious during attempts at sleep. (2) *Emotional instability* is observed, in which high spirits alternate with moodiness, laughter with tears, and not infrequently intense love with hatred. A happy medium,—a stability of feelings and emotions—a degree of the phlegmatic in temperament,—these are conspicuously lacking. (3) *Excitable heart with labile pulse* is common. These subjects are apt to present heart hurry on the slightest provocation, with or

without palpitation and an "out of breath" feeling. Occasionally, the heart rate is perpetually at a figure somewhat above normal, a characteristic of which the patient is rarely cognizant; but usually the normal rate obtains during repose. The pulse is soft, compressible, and often dicrotic, and frequently indicates a status of sinus arrhythmia. (4) *Vasomotor ataxia* is constant, as evidenced by the capillary pulse, dermographia, the tendency toward hyperidrosis, and sensations of undue heat of the surface of the body, even in cold weather. (5) *The eyes are brilliant or sparkling*, especially during conversation and active attention, when there may be observed at times even a suspicion of exophthalmos. In many instances an imperfect or larval von Graefe sign may be elicited. (6) An unusually *palpable thyroid gland* is almost constant in these subjects, though on inspection the thyroid area may appear merely somewhat full or even normal. A large percentage of these subjects are sufferers from puberty hyperplasia.

These persons are to be found everywhere,—more especially among Caucasians, whose mentality is at the highest state of development; in all strata of society, rich and poor, male and female, young and old; in all countries, and in almost all climes. While the greatest number may be combed out from the vast multitude of high school and college students, school teachers, stenographers, young business and professional men, real and would-be stock brokers, and the young newlywed;—the mill hand, the newsboy, and the laborer are not immune. All these are members of a community of mortals who have many things in common physically and mentally, namely, a generalized instability of the autonomic nervous system and of the chain of endocrine organs,—a lowered threshold of emotional and reflex activity, and an ever present danger of the development of an attack of the Basedowian syndrome.

Acquired Predisposing Influences are traceable to most of the acts of the body and mind of the individual. Born with a standard of physical and mental health at variance with that of his fellows, such a person will not find himself at an equilibrium with those circumstances in life which ordinarily are in entire agreement with the average person. These acquired predisposing factors occur from the very moment of birth and may continue on throughout existence, and unless the maladjustment is corrected through the interference of favorable influences, the persistence of this handicap may mean an attack of Graves' disease.

The Exciting Factors are far more tangible and traced with less difficulty than the predisposing causes. Most of these have already been mentioned. Given a subject of the type above described, place him in an automobile going at the rate of 40 miles an hour, and rush the machine across railroad tracks just in time to avert a collision with an approaching train, and the mechanism of Graves' disease is begun. There need not be an accident. Psychic trauma, with or without physi-

cal injury, is the most usual history obtainable as the starting point of Graves' disease. Following an earthquake, or a fire in a large factory in which many are employed, a massacre, the wreck of a liner in midocean, during action on the firing line in battle, or in other situations of imminent danger to life, forty-nine out of fifty persons soon recover physical and mental poise after their experience and are themselves again. One of them, however, because of the singular susceptibility, may evince no psychic and endocrine recoil or adjustment to the previous neuro-endocrine balance. The trembling, staring eyes, cold, clammy skin, heart hurry, and other features expressing fright, remain, become chronic or "frozen," and we are confronted with a case of Graves' disease. The torch of an exciting cause in the form of the acute emotional strain or psychic trauma applied to the inflammable subject means a beginning of the syndrome of the disease.

Certain circumstances characterized by less acute but more sustained emotional strain and which ordinarily serve as predisposing factors, are likewise exciting causes. Especially is this true if the predisposing errors in question become intensified, and if the susceptibility of the individual is unduly great. It is from this class of subjects, the small minority, that we fail to elicit a history of psychic trauma or acute emotional strain as the starting point of the syndrome. Extreme illness or the death of a loved one; emotion such as hate, anger, jealousy, and the prolonged strain of such occupations as school teaching, telephone operating and the like, unrequited love and sexual maladjustments may serve both as predisposing and exciting causes.

The following instances, taken at random from my files, will serve to illustrate the potency of emotional strain or psychic traumata as exciting factors of Graves' disease:

Case 1 is that of a business man, age 39, who developed a very virulent form of Graves' disease, following extreme worriment over business troubles.

Case 2 is that of a housewife of 42 who, shortly after her marriage 17 years before, developed a most severe form of Graves' disease following intense marital and conjugal incompatability.

Case 3 is that of a female of 30, in whom a severe form of Graves' disease developed several months after the announcement of her engagement.

Case 4 is that of a merchant of 39, on whom a friend played the practical joke of turning a hose pipe upon him from the rear, as he was seated in his garden one hot July afternoon. The syndrome of Graves' disease asserted itself very shortly thereafter.

In case 5, that of a housewife of 32, a very severe form of Graves' disease followed a week or two after an extreme shock, which was in the nature of a diminutive mouse that ran across her neck awakening her with a start out of a deep sleep.

Case 6 is that of a male of 50 who developed a severe form of the disease within a month after the shock of a son's suicide.

Case 7 is that of an iron worker, age 26, who, after unloading a car of gravel and becoming very much overheated, suddenly jumped into the Schuylkill River to cool off. Several days later, he began complaining of nervousness, large neck, and palpitation, and on looking into the mirror, discovered that his eyes were bulging.

Case 8 is that of a male of 47, employed by a telephone company, who developed a most malignant type of the disease almost immediately after a shock sustained through being a passenger in an elevator which dropped nine floors.

Case 9 is that of a male of 32 who was employed in a munitions plant in which an explosion occurred. Though he received no bodily injury, he was so badly shocked that he fell to the floor in a faint, and a few days later all the typical symptoms of Graves' disease asserted themselves.

Case 10 is that of a housewife of 22 whose typical syndrome of Graves' disease followed several exciting factors, among which were trouble with her mother-in-law, business reverses of her husband, and the extreme worriment of impending miscarriage on three different occasions during her first pregnancy.

Case 11 is that of a business man who, while driving an automobile, collided with a motorcycle. A month later, there developed diarrhea, nervousness, insomnia, extreme weakness, large neck, and bulging of the eyes.

Case 12 is that of a female of 25, an Ediphone operator, who developed a moderate form of Graves' disease, following worriment over relatives who were at the front during the World War.

Case 13 is that of a female of 25, in whom all the symptoms of the disease followed shortly after "an upsetting ordeal with a male friend."

Case 14 is that of a housewife of 34 who developed the syndrome shortly after the experience of undergoing a dilatation and curetttement without a general anesthetic.

Case 15 is that of a school girl of 16 who developed the typical syndrome of Graves' disease following attendance at her grandmother's funeral.

Case 16 is that of a housewife of 35 in whom the onset of the disease occurred shortly after the nervous tension incident to the ordeal of watching over her child who had undergone two mastoid operations.

Case 17 is that of a housewife of 29 in whom Graves' disease complicated by melancholia developed within a month after she attempted to extinguish a fire resulting from a gas range accident.

Case 18 is that of a housewife of 24, who developed Graves' disease a few weeks after the extreme shock and terror of being caught in a fire in a New York subway.

Case 19 is that of a housewife of 27 who developed a most severe

form of Graves' disease following the shock of being compelled to flee from her house during the night because of a fire which broke out in an adjoining house.

Case 20 is that of a business man of 40 in whom a virulent form of Graves' disease with extreme cardiac manifestations followed a period of family unpleasantnesses coupled with financial difficulties.

Case 21 is that of a housewife of 45 who was so badly scared over an attack of infantile paralysis in one of her children that she developed Graves' disease in an almost acute form.

Case 22 is that of a young woman of 20 who developed Graves' disease following a period of extreme tension incident to secretarial duties in a busy office.

Case 23 is that of a discharged doughboy of 24 who developed Graves' disease complicated with pulmonary tuberculosis following certain harrowing incidents on the firing line during the World War.

Case 24 is that of a domestic of 53 who had been "sensitive" all her life, and in whom a very severe form of Graves' disease followed employment under a scolding, irritable housekeeper.

Case 25 is that of a young married woman of 25 in whom Graves' disease developed shortly after the extreme shock of being informed over the telephone that her sister was killed in an automobile accident. It is interesting to note that though this message happened to be an error, the syndrome nevertheless advanced to its full manifestations.

The foregoing 25 instances are typical examples of exciting causes which are significant, and which are often missed in hasty history taking. It is obvious that the psychic factor in the pathogenesis of Graves' disease is strongly evident in the great majority of patients. So often is it encountered in my experience, that in the instance in which I fail to elicit it during the first consultation, it is usually gotten a short time thereafter, by the patient's recall to mind of some responsible emotional strain or psychic trauma which was omitted in the detailing of the history during the primary examination.

Excessive social obligations and instances of "high life" and its ambitions and other implications, discord with relatives and friends, misplaced or unrequited love, and intense emotions, as fright, grief, mortification, jealously, hatred,—all these should be the object of our investigation and correction as exciting factors of Graves' disease.

Such exciting causes as the infections and intoxications, pelvic neoplasms, and the miscellaneous factors, have already been mentioned.

In concluding these views on pathogenesis, it is relevant to remark that the syndrome to which we apply the term exophthalmic goiter is not *goiter*, and the sooner this affection is removed from the classification of *goiter*, the sooner will a rationalization of therapeusis be effected. While encapsulated nontoxic goiter and toxic adenoma are local conditions yielding satisfactorily to thyroidectomy, this cannot be said

of exophthalmic goiter, the etiology and especially the symptomatology of which is as widespread as the body itself. Every organ and its function, every tissue,—indeed, every cell of the patient is involved; and when thyroid swelling exists, it is not the cause of the disease, but incident to a series of events constituting the syndrome. Hence it is that in patients whose thyroids are not productive of marked pressure symptoms, whose vital organs are not too badly damaged, who are not insane, and in whom satisfactory coöperation is obtainable, the experienced individualizing internist obtains an unrivaled statistical showing.

Incidentally, history taking in patients with exophthalmic goiter is an art. The introspection, mental alertness, and other peculiarities encountered mean that the medical attendant must not only devote at least two hours to the task of taking the history and making a physical examination, but tact, diplomacy, and patience must be exercised in the process. It is often best to complete the records in two periods.

In keeping with the neuro-endocrine theory as a practical working basis in the history taking and examination of these patients, I here-with submit the history and examination forms I am using in my work.

HISTORY

Case No..... Date..... Referred by.....
 Name..... Address..... Age..... S.M.W. Occupation.....

*Chief Complaints:**Family History of*

Thyroid enlargement?	Epilepsy?
Diabetes?	Chorea?
Bronchial asthma?	Insanity?
Nervous indigestion?	Paroxysmal tachycardia?
Tuberculosis?	Raynaud's disease?
Neurasthenia?	Angioneurotic edema?
Hysteria?	Paralysis agitans?
	Miscellaneous:

Previous Medical History:

Diseases of childhood:
 Diseases since childhood:
 Venereal diseases:
 Child birth, operations, accidents, shock, etc.:

Social and Personal History:

Incidents of puberty:
 Incidents of school life:
 Sexual life:
 Home environments:

Habits:

Food:
 Drink:
 Tobacco:
 Drugs:
 Personal hygiene:

Occupational factors:
 Business and other cares:
 Relations with companions and friends:

Psychological Peculiarities:

Temperament:
 Accomplishments and ambitions:
 Repressions:
 Obsessions, fears, frights:
 Sleep:
 Dreams:
 Miscellaneous:

Present Illness:

Approximate date and mode of onset:
 Nervous Symptoms:
 Circulatory Symptoms:
 Ocular Symptoms:
 Neck Symptoms:
 Gastrointestinal Symptoms:
 Respiratory Symptoms:
 Genitourinary Symptoms:
 Cutaneous Symptoms:
 Miscellaneous Symptoms:

Previous Medical or Surgical Treatment:

PHYSICAL EXAMINATION

Sex.....	Race.....	Apparent Age.....	Weight.....	Height.....	Facies.....
State of Nutrition.....		Temperature.....	Pulse.....	Respiration.....	Bl.Pr.....
<i>Skin:</i> Dermographia?.....	Hyperidrosis?.....	Eruptions?.....		Miscellaneous.....	
Mucous Membranes:.....		Lymphatic Glands:.....			
<i>Mouth:</i> Tongue.....		Teeth.....		Gums.....	
<i>Tonsils:</i>			Pharynx.....		
<i>Nose:</i> (Obstructions, etc.).....					
<i>Eyes:</i> Exophthalmos.....	Dalrymple's Sign.....	Kocher's Sign.....	Moebius'.....		
Stellwag's Sign.....	Von Graefe's Sign.....	"Hitch Sign".....	Dryness.....		
Moisture.....	Vision.....	Brows and Lashes.....	Eye Grounds.....		
Ocular Bruit.....			Miscellaneous.....		
<i>Neck:</i> Circumference.....		Superficial Veins.....	Vascular Throbbing.....		
<i>Thyroid Gland:</i> Goiter?.....		Contour.....	Throbbing.....		
Consistency.....		Tenderness.....	Compressibility.....		
Thrill.....		Bruit.....	Miscellaneous.....		
<i>Chest:</i> Respiratory Expansion (Measurement):.....					
(Lungs) Inspection:.....					
Palpation:.....					
Percussion:.....					
Auscultation:.....					
X-Ray Examination (Include substernal or accessory goiter, thymus, heart, lungs):.....					
<i>Heart:</i> Inspection:.....					
Palpation:.....					
Percussion:.....					
Auscultation:.....					
<i>Abdomen:</i> Inspection:.....					
Palpation:.....					
Percussion:.....					
Auscultation:.....					
<i>Limbs and Tendon Reflexes:</i>					
<i>Tremors:</i>					
<i>Psychic Status:</i>					
<i>Laboratory Findings:</i>					
Pulse Tracings:.....			Urinalysis.....		
Blood Examination: Red blood corpuscles.....	H.B.....		White blood cells.....		
Differential.....	Blood Sugar.....		Wassermann reaction.....		
Basal Metabolism:.....					
Quinin Test:.....					
Goetsch Test:.....					
Pituitary Test:.....					

Final Diagnosis:

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CHAPTER IX

SYMPTOMATOLOGY OF EXOPHTHALMIC GOITER

IN the consideration of the clinical manifestations of exophthalmic goiter, it is interesting to note Dr. Graves' own description of the disease as it was published in 1835: "A lady, aged twenty, became affected with some symptoms which were supposed to be hysterical. This occurred more than two years ago; her health previously had been good. After she had been in this nervous state about three months, it was observed that her pulse had become singularly rapid. This rapidity existed apparently without any cause and was constant, the pulse being never under 120, and often much higher. She next complained of weakness on exertion, and began to look pale and thin. Thus she continued for a year, but during this time she manifestly lost ground on the whole, the rapidity of the heart's action having never ceased. It was now observed that the eyes assumed a singular appearance, for the eyeballs were apparently enlarged, so that when she slept or tried to shut her eyes, the eyes were incapable of closing. When the eyes were open the white sclerotic could be seen to a breadth of several lines all around the cornea." Graves did not mention the tremor; this sign was described by Charcot some years later. Graves little dreamed of the complex disease he was describing, nor did he realize what lengthy discussions and many volumes would follow in the wake of his modest though epoch-making paragraph.

In no other disease in the domain of medicine is the symptomatology as varied and the clinical manifestations as widespread as in exophthalmic goiter. No description of clinical phenomena can completely portray the physical and mental subjective and objective manifestations. As best, a writer can describe with mere relative accuracy the syndrome to which so many observers are now devoting their best attention, for there are so many types of departure from the average case that even a large volume devoted to the subject of symptomatology alone would perchance leave many things unmentioned.

In this chapter we shall briefly survey the symptomatology of (1) acute Graves' disease; (2) the incipient or *fruste* form of the disease; (3) the usual or chronic type; and (4) atypical forms of Graves' disease.

1. ACUTE GRAVES' DISEASE

Fortunately, the acute or abortive type of Graves' disease is rare. The course is brief and malignant, and there is very rapid loss in weight. Extreme tachycardia, hypertension, distressing palpitation, and the various forms of arrhythmia are common. Hyperpyrexia is occasionally present, with severe nausea, vomiting and diarrhea. Hemoptysis and melena may occur. Exophthalmos is marked, and trembling of the entire body may be so severe as to cause vibration of the bed upon which the patient lies. The basal metabolism may be anywhere from plus 75 to plus 150 or more, and the patient may lose as much as one-half the body weight within a few weeks. The most tragical symptom is the mental derangement commonly seen in these patients. Acute delirium, dementia, or mania, coupled with the incessant nausea and vomiting, may lead to death from collapse and exhaustion.

Finkle reports 4 cases of acute exophthalmic goiter whose most marked symptoms were tachycardia and rapid and excessive loss of weight. He emphasizes the fact that in no other disease does the patient lose so rapidly in weight,—in a case of Schlesinger's 122 pounds in eleven weeks, in one of his own patients 48 pounds in a few days, and in another 110 pounds in a few months. There was no enlargement of the thyroid in 2 cases and none in the beginning in another case in which later a large goiter developed. The tachycardia was constant and in some became a perpetual irregular arrhythmia; the blood pressure also ran up extremely high. Fever of a remittent type was occasionally observed, especially in a case accompanied by motor disturbances resembling the severest type of chorea, persisting for some time after subsidence of the other symptoms. In addition to the clonic spasms in this case there was also contracture of the hands, suggesting tetany. The onset in one case simulated severe gastro-intestinal poisoning.

An acute exacerbation of the usual chronic form of the disease may follow thyroidectomy and is often seen by thyroid surgeons. This is a common cause of post-operative death. Crile, Crotti, Chesky, Major, and others have attributed the acute post-operative exacerbations to acidosis. During the course of the operation or immediately after, often as the patient comes out of the anesthetic, he is seen to undergo a state of great excitation with marked delirium, exaggerated tremor, extreme anxiety, drenching perspiration, and, at times, hallucinations and mania. The pulse mounts up to 180, 190 or even 200, soon becoming feeble and impalpable; there is high fever, vomiting and incontinence of urine and feces, usually terminating in fatal collapse within a day or two. Rarely a case of this sort recovers.

Again, acute Graves' disease, though not quite as severe as in the primary type, is observed in the period of crisis during the course of

the usual form of the affection. Many patients do not present crises and remissions; a large percentage do. At this time, usually a period of two or three months' duration, all the symptoms become accentuated, and there may appear many new phenomena. The basal metabolism and heart rate are increased, the weight is further reduced, mental symptoms are apt to become pronounced with an occasional onset of insanity, and the gastro-intestinal symptoms, especially nausea, vomiting, and diarrhea, may in themselves endanger the life of the patient. Such a subject may become physically and mentally helpless, requiring extremely careful nursing and therapeusis. It is at this time that the morale of all concerned, even of the family physician, is weakened and often lost.

A similar, often worse condition of affairs is observed when, during the course of the disease, and even when the patient is improving, there is superimposed another psychic trauma or shock, such as an automobile accident, the sudden death of a relative, a narrow escape from a conflagration or other situations of sudden extreme peril or emotional strain. I have observed quite a number of such instances, and the clinical picture is often tragic to behold. A formerly mild case becomes a severe one; a sane patient may become insane; an organically good heart may undergo acute dilatation, or begin to fibrillate badly, and a patient in whom the prognosis appeared excellent may become moribund. In most instances of this sort, tactful, expert nursing, with insistence upon a military discipline in coöperation of all concerned, will reclaim the patient to a favorable course of the disease and ultimate recovery.

2. THE EARLY, INCIPIENT OR "FORME FRUSTE" TYPE OF GRAVES' DISEASE

As in tuberculosis and other chronic affections, there is in Graves' disease an early period in which the clinical picture is mild, indistinct, vague, doubtful, and frequently misleading. Also, as in tuberculosis, diabetes and other affections, so in Graves' disease we note that there are thousands of individuals affected, but who, unconscious of their danger, go about their respective duties apparently unhindered by their affliction. The subjective symptomatology is not quite urgent enough to force the patient to seek medical attention. There are far more cases of unrecognized incipient and even frank Graves' disease than are suspected by the medical profession at large. Hemmeter, for instance, makes the following statement: "Professor Hamburger, President of the last international congress on physiology, in studying the increase of hyperthyroidism (exophthalmic goiter?) in the army in Holland, found it to be 10 percent. Among the German people it was 8.5 percent. It will soon be seen in this country in the nature of an epidemic,

and preparation must be made to meet it. Ten per cent. of an army of a million means 100,000 cases." In recent years, when refinements in diagnosis and laboratory procedures have revolutionized our modes of procedure in hospital and out-patient clinics, we are beginning to realize that the incidence of early, mild and even advanced cases of Graves' disease that have heretofore escaped attention is enormous, and far from being a rare disease, this affection is recognized as being more common than carcinoma. As mentioned elsewhere in this work, the thousands of cases from the ranks of the soldiers of the World War, labeled with such diagnoses as "shell shock," "effort syndrome," "neurocirculatory asthenia," and the like, are in the majority of instances early or atypical forms of Graves' disease.

Early, formative, or borderline cases, instances in which the diagnosis offers many pitfalls, may appear and be diagnosed as neurasthenia, hysteria, nervous indigestion, "nervous breakdown," early phthisis, cardiac neurosis, "shell shock," and many other conditions. These so-called *forme fruste* cases may be further subdivided according to the clinical course into the following varieties:

(a) Progressive or aggravated puberty hyperplasia, the mild neuroendocrine dysfunction characterizing puberty and adolescence, which may develop slowly or suddenly into frank Graves' disease, but in which there may occur spontaneous recovery. This condition is described elsewhere.

(b) The early or mild form of Graves' disease which remains permanently as such, all things being equal. For example, a young girl during the adolescent stage, often during attendance at college, begins to experience daily sensations of heat, and there arises a tendency to diarrhea. Sleep becomes restless, there is some loss of weight, and she becomes irritable and lachrymose on the slightest provocation. There may be a slight fullness of the thyroid which is more noticeable during menstruation, some palpitation, and the eyes are large and brilliant. These symptoms may disappear without treatment within several months or a year, but often they progress toward the development of a typical clinical picture of exophthalmic goiter.

Again, under the stress of business pressure, a young man having deprived himself of all recreation for a protracted period, begins to suffer with indigestion. He applies for treatment but his case is refractory to ordinary therapeutic measures, and within a short time not only are his subjective symptoms intensified, but he finds that he cannot sleep and feels so irritable and restless that he fears he is losing his reason. His heart feels rather uncomfortable, especially after eating; he is somewhat "short of breath" and is losing weight rapidly, though eating as much as usual. Finding that his collars are becoming a little tight, he soon discovers that his neck is somewhat full in front and hurries to advise his physician of the fact. Physical examination re-

veals a slightly hyperplastic thyroid, heart hurry, and perhaps a tremor of two or three fingers.

As described in the chapter on Pathogenesis (neuro-endocrine theory), these persons form a distinct class of humanity. They are usually young adults leading an active mental life, who present a significantly higher pulse than normal,—perhaps 80 or more when quiet, which, on the slightest physical or mental excitation, may rise to 100 or more, with a tendency toward dyspnea. The skin is plethoric, thin, soft and moist; dermographia is present; there is great tolerance for winter months and poor tolerance of summer heat; there is a tendency toward hyperchlorhydria; the eyes are brilliant; the thyroid is unduly palpable; the appetite is excellent; the weight is usually about 10 pounds below normal but may in some instances be 15 pounds above their normal standard; reflexes are hyperactive, there is a very fine tremor of the outstretched fingers, and there is a tendency to cerebral hyperactivity and emotionalism. From a casual observation, these persons are neither normal nor quite abnormal. Many of them are subjects of puberty hyperplasia. They are capable of earning a livelihood, especially in mental pursuits, and often appear in the pink of health. Their mental characteristics may earn for them such appellations as "touchy," "bright," "talented," "genius," "nervous," "thin-skinned," "devoted," and other terms indicating sentimentality, emotionalism, tenseness of purpose, and often instability of disposition.

(c) The early stage of the *usual* or *progressive* form of Graves' disease may appear in the manner just described, the manifestations becoming accentuated during the course of several weeks or months until the frank syndrome of the affection is developed.

3. THE USUAL FORM OF GRAVES' DISEASE

In a small minority of cases the usual form of the disease is of sudden onset, occurring as a lightning bolt out of a clear sky. Thus, after a sudden psychic trauma, or emotional strain or fright, with or without physical injury, instead of the usual weeks or months of formative period, the syndrome will appear at once. In one of my patients the frankly outspoken clinical picture occurred in a man of 32, a munitions worker, immediately after an explosion in a building within a block from the place where he was at work; the shock rendered him unconscious, and shortly after he was picked up, there was severe hyperhidrosis, tachycardia, trembling and exophthalmos. In another instance, a young woman developed the disease immediately after a fall from a ladder. In still another, an automobile accident was the cause of an immediate onset of the disease in a man of 40 who was not at all injured physically.

Ordinarily, the disease develops insidiously after the superimposi-

tion of an exciting factor upon a lifelong susceptibility. After several months to a year or more of gradually accumulating subjective and objective phenomena, the patient may appear in the doctor's office complaining merely of muscular weakness, and loss of weight; or the chief complaints may be occasional palpitation, nervousness, and insomnia; or in some instances the dominant subjective feature may be frequent diurnal and nocturnal micturition which causes the subject to suspect diabetes or Bright's disease. Occasionally marked sweating, especially at night, will become so regular and exhausting that the patient will fear the existence of tuberculosis and will consult the physician with this diagnosis in view. Not infrequently the patient will refrain from seeking medical attention until the thyroid has become very perceptibly swollen, or exophthalmos has developed. Occasionally, goiter is the only subjective complaint, and the patient, stimulated by the causal toxins, claims to be "feeling fine" until the understanding internist, questioning him regarding loss of weight, heart hurry, hyperidrosis, weakness in the legs, trembling and insomnia, will surprise his subject and elicit positive responses to all these and other symptoms. It is just then that the object of the doctor's attention may realize that he is really a patient and has been sick for some time.

Heart hurry is a constant and conspicuous feature of the disease and, in combination with weakness and precordial distress, may precede the other cardinal symptoms for a variable period of time. The heart rate may be 90 to 140 or more per minute, frequently accompanied by palpitation and dyspnea, a combination of symptoms for which alone the subject often seeks relief.

Goiter may be absent for a while or appear in variable degree with the onset of other cardinal symptoms. Often the thyroid gland maintains its normal size during the course of the disease. In Graves' disease the increase in size is rarely great enough to produce marked pressure symptoms. In a small percentage of cases the patient becomes aware of a swollen thyroid only after discovering that the clothing about the neck becomes too tight. Usually, thyroid swelling occurs some time after other frankly outspoken evidences of the disease have appeared.

Exophthalmos or protrusion of the eyeballs, usually bilateral, is present in the majority of cases and occurs at a variable time following the appearance of other symptoms significant of the disease. The degree of exophthalmos varies with the severity of the case and in the same individual at different times. Associated with these symptoms, the von Graefe, Dalrymple, Stellwag, Moebius, and other eye signs may be observed.

Tremor is always present and may exist as an early sign. It is fine, involuntary, and obtained by having the patient extend the arms and stretch the fingers apart. Along with the tremor may be observed nervous disturbances of varying degree, *viz.*, insomnia, mental excita-

tion or depression, neurasthenia, hysteria, melancholia, and rarely one of the psychoses.

Miscellaneous Symptoms.—One of the most prominent manifestations of Graves' disease is the extreme susceptibility of the patient to fatigue. He feels weak, the thigh and calf muscles feel as though they have been inactive for months, and though ambition is normal or excessive, there is no physical or mental support to action, and the patient feels "all in." Flexor and extensor muscles of the calves and thighs feel as though they have been beaten; they are sore, demand rest, and when the patient endeavors to recline, he discovers that his hands and feet tremble. In brief, though the patient seeks repose, he finds to his dismay that complete rest is impossible. It is often observed that most of the symptoms of Graves' disease are aggravated by lying down, and that these patients, far from feeling refreshed by a night in bed, arise in the morning feeling worse than ever.

The marked bodily wasting is not only an early symptom of Graves' syndrome but is a progressive and conspicuous accompaniment of the other manifestations during the entire course of the disease. The increased metabolic rate varies widely. In some cases the rate may reach + 75 or even + 100 percent. or more above normal. Thus a patient formerly strong and robust becomes within a few months or a year or two, a weak, tired creature, often more emaciated than if he were affected with an advanced stage of diabetes mellitus or phthisis.¹

COURSE OF GRAVES' DISEASE

The course of the average case of Graves' disease depends upon many circumstances, the most important of which are the age, sex, the condition of the patient before the onset of the disease, the severity and duration of the disease, the presence or absence of intercurrent or complicating affections and many other factors, including the mode of treatment adopted. These are discussed in detail in the chapter on the Prognosis of Exophthalmic Goiter. We shall here mention a few facts in the clinical picture as they present themselves during the progress of the disease, confining ourselves to *untreated* patients.

¹With respect to the congenital form of the disease, Sainton and Delhern have described a form of hyperthyroidism characterized by a hyperesthesia or a natural hyperexcitability peculiar to women, manifesting itself under the effect of any emotional trouble whatever by slight exophthalmos with peculiar brightness of the eyes, swelling of the neck, frequency of heart beats, and a stage of light tremor. Stern has attempted to isolate a type of the disease called "Basedowites." These are persons with hereditary nervous predisposition and in whom towards the age of twenty years appeared a Basedowian syndrome somewhat masked: palpitation with pain, small goiter soft or resisting, with colloid nodosities, but causing a very keen embarrassment, spasmodic dyspnea, tremor, rapid pulse, but under 120. These patients are never cured, but on the other hand never become true Basedowites. According to Falta, however, this form predisposes to true Graves' disease.

In the usual patient, the clinical symptoms occur somewhat in this manner:¹ A few days, weeks or months following the incidence of an exciting cause, there is a gradually oncoming feeling of weakness, especially in the calves of the legs, and a gradual loss of weight and strength. Shortly thereafter the patient begins to experience precordial distress and palpitation, especially on physical or mental excitation. At this time, if the patient be a man, he will discover that the collars which he has been wearing are becoming too tight and he will begin to suspect that there is a slight swelling over the front of the neck. Soon the members of the family or friends will observe a change in disposition and a marked tendency, on the slightest provocation, to a disturbance of the usual mental poise. By and by the patient or friends will observe a peculiar stare in the expression not unlike a degree of fright or terror, which soon manifests itself as a distinct bulging of the eyes; and in the course of time, or possibly during the incidence of the foregoing manifestations and hitherto unobserved, the tremor of the outstretched fingers will be noticed. The blending of one cardinal symptom into the other or their superimposition may require weeks or months, but there is a certain duration of time necessary to have them all noticeable concomitantly as a *typical* picture of exophthalmic goiter. It is the transitional stage between the first symptoms and the occurrence of all the rest that offers many pitfalls to the general practitioner in the diagnosis of the case. The above is the usual course of events in a typical case of the disease.

Remissions and Crises.—Though in many untreated patients with typical Graves' disease the course of the affection progresses to a clinical picture of definite severity, at which point the syndrome remains stationary until circulatory or psychic imbalance or sequences complicate the situation, in the majority of instances the syndrome, instead of remaining more or less stationary, evinces periods of remissions and crises. The symptoms, at first more or less uncertain, gradually become clearer and more severe until, when the ninth month after the appearance of at least tachycardia and tremor is reached, the manifestations of the disease become rather intense, and the patient has reached what may be termed a *crisis* in the disease. This period of extreme toxemia is of variable duration, and the patient may die of an overwhelming excitation of the circulatory and nervous systems. Usually there is a slight lull or remission within another few months, which lasts approximately until the eighteenth month, and the patient may again become improved until the twenty-second to the twenty-fifth month, when the symptoms are again aggravated, but not quite to the extent seen during the first crisis. This exacerbation may lead to death from a psychosis or cardiac complication, but usually the patient rises above

¹This is an abstract presentation; there are innumerable variations in the mode of development of the frank manifestations of Graves' disease.

this critical period within a few months, after which another remission of moderate degree of improvement sets in. Aside from an occasional moderate exacerbation of the symptom complex brought on by physical or mental deleterious factors, the signs and symptoms of exophthalmic goiter in the average case remain more or less constant after the thirtieth month of the disease.

It must be stated, however, that the degenerative processes from the persistent irritation and hyperoxidation of bodily structures lead to an increasing state of invalidism. This is of two kinds, first, that of hypo-



FIG. 65.—Exophthalmic goiter without exophthalmos; weight 152 pounds; pulse rate 140; circumference of neck 15½ inches.



FIG. 66.—Same patient as in Fig. 65, three weeks later. Result of added psychic trauma incident to the death of her infant. Development of exophthalmos; loss of 15 pounds in weight; pulse rate 160; extreme emotionalism and restlessness.

thyroidism, due to the "burning out" of the thyroid, second, which is most usual, the invalidism of the incessant toxic processes leading to degenerative metamorphosis of circulatory, nervous, renal and other structures. Depending upon the predominating symptoms, these cases are at times referred to as "cardiac types" or "nervous types" of Graves' disease. Other "types" of the disease are occasionally mentioned.

Exacerbations occurring during a favorable progress of events may follow a superimposition of an exciting factor. Thus, in a patient with a moderate syndrome of Graves' disease, the meeting with an automobile or trolley accident is very likely to result in an acute exacerbation of the disease amounting to a severe crisis or an attack of acute Graves' disease in some instances.

Spontaneous Recovery occurs in so few instances, that such an event is hardly to be expected in a given patient. To expect this is an extreme case of taking a gambler's chance, as it does not happen in more than 2 or 3 percent. of cases. Many instances of so-called natural or spontaneous recovery from Graves' disease are not recoveries. They are (a) instances of actual Graves' disease in the stage of remission; (b) very chronic cases of many years' suffering in which the tissues have gained a partial immunity to the etiological toxins, and the patient is enjoying a degree of *relative* improvement; and (c) instances of developing or actual hypothyroidism from thyroid degeneration.

Intercurrent Infections usually have a deleterious but at times a beneficial influence upon the course of Graves' disease. In most instances, the onset of such conditions as influenza, typhoid fever, infected tonsils, teeth, and the like, aggravates the symptomatology to the breaking point. Occasionally, the reverse is true, and we observe that an attack of rheumatism, quinsy, typhoid fever, or other infections, leads to marked improvement of Graves' disease, and occasionally to an apparent cure. For instance, Squier reports two cases in which complicating infections first caused a marked increase in the severity of the Graves' syndrome, which was later followed, after the acute infection had subsided, by striking improvement and a disappearance of symptoms. Hale-White mentions the case of a woman who was admitted to the hospital for operation for exophthalmic goiter; after she had been in a few days and before the operation, evidences of typhoid fever were observed. She was transferred to the medical ward, and there, following recovery from the typhoid fever, it was observed that all the evidences of Graves' disease had disappeared. Beck, Vincent, and others have made observations of similar nature. In instances in which the intercurrent infection leads to an enforced rest in bed for a considerable time, marked improvement of Graves' disease is a strong possibility.

The Inherent Neuro-Endocrinopathic Make-up, the nature of which we know very little, probably bears a strong relationship to the course of the disease, *i.e.*, whether the syndrome will be light or severe, brief or protracted, and probably determines which organs or tissues will become the seat of greatest morbid activity and damage during the progress of the syndrome. Why are some patients free from thyroid enlargement and exophthalmos while others suffer with large neck and bulging eyes? Why is one patient free from severe gastro-intestinal disturbances while another is afflicted with nausea, vomiting, and diarrhea which dominate the symptomatology and endanger life itself? Why are some patients free from sugar intolerance while others present evidences of diabetes? Why does one patient remain rational while another becomes insane? Why does the circulation in one patient maintain its equilibrium while in another there is decompensation and anasarca? These and many other questions in the consideration of the clinical picture of Graves'

disease may be variously explained. Vagotonia, sympatheticotonia, dysthyroidism, or a combination of these and various other theories may assist us in an analysis of a given clinical picture. One thing, however, is probable: There is a strong likelihood that the disease affects with greatest intensity that part or system of the body most vulnerable to its attack, and in this statement must be included vulnerability due to the stigmata of hereditary as well as acquired factors. These implied reasons seem to be responsible for the various *atypical* forms of Graves' disease, described elsewhere.

Having briefly discussed the clinical picture of Graves' disease a detailed description of the symptomatology of the disease will now follow.

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CHAPTER X

CIRCULATORY SYSTEM IN EXOPHTHALMIC GOITER

CIRCULATORY phenomena are constantly present in Graves' disease. There is no Graves' disease without heart hurry. Unfortunately, *heart* remedies *per se* do not overcome the tachycardia of Graves' disease but usually aggravate the condition. On the other hand, measures hardly classified as heart remedies but which effect a general improvement of the patient's syndrome, cause a slowing of the heart through an amelioration of causal factors. It is not the heart but the disease which calls for treatment.

It is the circulatory system, especially the heart, which indicates the severity of the disease and its probable previous duration. In this respect circulatory findings are as reliable as basal metabolism determinations. During observation of the patient these findings indicate the course and prognosis of the disease. If the disease remains untreated or neglected, the circulatory system is usually the cause of death; if properly managed, it is the return of the circulatory system to normal function that indicates recovery of the patient. The medical attendant cannot give the circulatory symptoms too much attention, as upon them depends much that is of vital importance to his charge.

THE HEART

The term *goiter heart* applies not only to the heart in Graves' disease, but also to the heart of patients with other types of goiter. Some observers claim that the heart is affected by all goiters. It is my impression that this is a somewhat overdrawn view. We have all seen goiters of protracted duration in persons of advanced age in whom the heart action, aside from changes due to age, is normal. Ordinarily, two types of goiter heart are recognized:

(1) **Mechanical Goiter Heart**, resulting from compression upon the great vessels by an intrathoracic goiter, with consequent cardiac embarrassment. Also, compression upon the trachea impedes pulmonary circulation, further embarrassing cardiac function. Some of the common pressure symptoms of intrathoracic goiter are altered voice, headache, dyspnea, vertigo, palpitation, and in course of time, hypertension and the symptomatology of myocardial degeneration.

(2) **Toxic Goiter Heart**, due to thyrotoxemia and probably also to neurogenic causes. Toxic goiter hearts are to be subdivided into (a)

those due to hyperthyroidism or toxic adenoma, a state of thyrotoxemia superimposed upon an old-standing simple or nontoxic goiter, and (b) those occurring in Graves' disease, in which hyperthyroidism is a mere link in the chain of events constituting the syndrome known as exophthalmic goiter.

We might go farther and describe a blending or combination of the types of goiter heart. For example, in a patient suffering with a mechanical goiter heart, thyroid hyperactivity may supervene. Occasionally a patient with a simple goiter may develop Graves' disease, not necessarily depending upon the preexisting adenoma. Again, in a subject of Graves' disease heart, the thyroid swelling may be intrathoracic or substernal, causing pressure symptoms which give rise to mechanical cardiac difficulties as well.

The Heart in pre-Graves' Disease Subjects.—It is well known that there are thousands of persons apparently normal, performing their daily duties, but who have a greater predisposition to tuberculosis than their fellows. On some such provocation as an attack of influenza, prolonged worriment, overwork, and the like, there develop within a short time frank manifestations of phthisis. The same may be said of Graves' disease. There is a percentage of humanity predisposed to Graves' disease which, though apparently normal, if placed in a position of mental stress or emotional shock, or trauma incident to situations in which the instinct of self-preservation is brought to the fore, as for example, a shipwreck, an automobile accident, a conflagration, and the like, slowly or suddenly develops a frankly outspoken clinical picture of Graves' disease. In the absence of such provocation such an individual would live in apparent good health through a normal span of existence. As mentioned elsewhere, these subjects, usually adolescents or young adults, are exceptionally keen in mentality and are frequently regarded as precocious. It is from this class of persons that arise a percentage of our poets, musicians, artists, and idealists. Now, it is here that we might begin to discuss the cardiac manifestations relative to Graves' disease. These persons are liable to a flaring up of the heart's action on the slightest provocation, with an increase in rate up to 80 or 100 per minute, with or without a degree of palpitation or dyspnea. The skin is apt to be somewhat flushed and moist, and dermographia is easily elicited.

The Heart in Incipient Graves' Disease (*Forme Fruste*).—The pre-tubercular subject, advanced a step farther, is the patient with incipient tuberculosis; we progress a step farther with a pre-Graves' disease subject, and we are presented with what is known as the *forme fruste* type of Graves' disease. Instead of being merely predisposed to the disease, the patient actually presents it in incipient form, consciously or unconsciously. There is a sparkle in the eyes, a tenseness of expression, a quickening of mentality; the vegetative functions are in a state of

moderate excitability, there is dyspnea and fatigue on moderate exertion, usually a loss in weight, but withal, aside from a consciousness of the heart action and palpitation, the patient may claim to be "feeling fine." Physical examination usually reveals an imperfect von Graefe's sign, an unduly palpable thyroid gland, an unusually moist skin, especially the palms of the hands and soles of the feet, always a tremor and dermographia, and a heart rate of 90 or 100 per minute. On moderate physical or mental strain, however, the rate may reach 140 or more. The heart impulse is more violent than normal, though there is no increased ventricular area. A degree of heart hurry is present even while asleep, amounting to possibly 100 cycles per minute.

The Heart in Outspoken Cases of Graves' Disease.—Graves' disease may develop acutely, that is, within a day or several days to a week or two following an exciting cause; or its evolution may be gradual, beginning with an incipient type. Usually goiter and exophthalmos are present, giving rise to a picture of frozen fright. In this scared-looking, undernourished though fat-necked, moist-skinned, weak-kneed, trembling, keen-minded, though often illogical and erratic patient, we are presented with cardiac manifestations that demand our attention and cause the internist no little anxiety.

At first the patient may be unaware of the heart hurry. Commonly there is more or less palpitation on exertion. It is important to note that whenever a patient without fever and without organic heart lesions, complaining of precordial discomfort, presents a persistent inexplicable tachycardia, Graves' disease should at least be suspected, irrespective of the presence or absence of thyroid swelling or exophthalmos. The severity of palpitation does not always depend upon the severity of tachycardia; moderate tachycardia may coexist with severe palpitation, and a patient with severe tachycardia may not complain much of palpitation. It is this consciousness of the heart's action with its perpetual thumping that may bring the patient to the doctor with a preconceived diagnosis of heart disease. Palpitation is also responsible for an exaggeration of the nervousness, for many patients, convinced of the presence of serious heart trouble, are in constant fear of impending death. This symptom is markedly increased on physical and mental excitation. A varying degree of dyspnea is present, and a sensation of trembling and restlessness, with poor, unrefreshing sleep. A rather constant complaint is the inability to sleep on the left side of the body because of the violence of the heart action and throbbing of the vessels of the neck and ears. Soon the palpitation becomes constant, with occasional sensations of precordial flutter and distress. At times, the precordial pains may lead to attacks simulating angina pectoris. This symptom may become so severe as to lead to a fear of sudden death, causing the patient to send for the medical attendant at any hour of the day or night. Rarely, attacks of genuine angina pectoris, with or without un-

consciousness, may occur. This is most apt to occur in male subjects with a plus Wassermann reaction or with a history of chronic alcoholism or nicotine poisoning.

Objectively, the precordium, the thyroid gland, vessels of the neck and elsewhere, and in fact the entire body may vibrate synchronously with the cardiac cycles. The capillary pulse is easily elicited. The bounding heart shows a strong tendency toward increasing hypertrophy, and the apical impulse is violent and heaving. Exertion at this time may lead to a considerable increase of cardiac dulness especially to the right. In the course of events, the forcible apical first sound shows evidences of beginning myocardial exhaustion. On physical examination, it is observed that cardiac hypertrophy and dilation occasion a diffusion of the apex beat, even extending into the left axillary space. On palpation a thrill is frequently elicited, especially in the presence of mitral insufficiency. Percussion, which during the early stages presented little of importance, now plainly indicates a heart enlarged in varying degree. The percussion note must discriminate cardiac enlargement from the frequently observed enlarged thymus. Auscultation confirms inspection, presenting at first a very forcible apical beat with or without a hemic murmur; later as dilatation occurs the sounds become weaker, lose their muscular tone and may present the various murmurs associated with myocardial fatigue. The pulse rate may vary between 100 and 140 to 160 per minute. At first full and dicrotic, soon with beginning myocardial exhaustion it loses some of its volume and force and may become arrhythmic. The heart, whipped on and on, unchecked in its mad rush during a period of months or years, begins to show signs of marked degeneration and dilatation. Thus we reach

A Heart in Advanced Graves' Disease, in which the rate has been double the normal for four, five, and occasionally ten years or longer. Dyspnea is now so markedly increased that shortness of breath may become a dominant subjective complaint. Compensatory hypertrophy and dilatation, first of the left ventricle, with the murmur of mitral insufficiency, may be followed by involvement of the other heart chambers. Either prior to or at this time, auricular and ventricular extrasystole, pulsus alternans, auricular flutter and fibrillation may occur. A continuation of this process leads to further cardiac embarrassment, decompensation, marked rise in venous pressure with the veins becoming more prominent and presenting systolic pulsations, pulsating liver, and anasarca—the most usual termination of untreated progressive Graves' disease. The end may occur within from two to ten or more years, depending upon the former condition of the heart, the severity of the affection, the presence or absence of complications, and the possible occurrence of periods of spontaneous or induced amelioration of the disease during its course. The evolution of cardiac hypertrophy, dilatation and decompensation in this disease occurs with the same sequence

as in the common forms of organic heart disorders, except that in Graves' disease these changes are usually more rapid. It is interesting to note that heart block rarely if ever occurs as a result of Graves' disease.

The cause of myocardial damage, as mentioned in the chapter on Pathology, is probably exhaustion from overwork, and to a lesser extent

the direct effect of toxins upon the heart structure. The heart pathology in Graves' disease is essentially interstitial myocarditis. There is some destruction of muscle fibers and round cell infiltration between the muscle fibers and about the blood vessels. Occasionally, in the very toxic cases with sudden death, myocardial necrosis, diffuse or focal, has been observed.

Characteristics of the Tachycardia.

The heart rate in Graves' disease may vary from 90 per minute in the *forme fruste* type to 180 and even higher in the very severe form of the affection. Of course, in the presence of auricular fibrillation, it may be impossible to compute the actual heart rate. The cause of the tachycardia is still uncertain. The fact that the administration of thyroid extract to a normal subject is capable of accelerating the heart's action is the basis of the argument of those who believe that

FIG. 67.—Severe Graves' disease of 10 years' duration, with impending circulatory decompensation. Note edema of eyelids and dilated veins over the thyroid.

Graves' disease, with its tachycardia, is due to thyroid hyperactivity. Hyperthyroidism is probably a partial cause of tachycardia in Graves' disease, but there are many other clinical features which, implying a much more complex etiology, indicate a complex causation of heart hurry. In addition to direct stimulation of the myocardium by thyroid hormone and probably other toxins originating elsewhere in the body, tachycardia of Graves' disease is probably due to stimulation of the sympathetic or accelerator nerve fibers and the diminished arterial tonus through peripheral vascular dilatation. Though the vagus is likewise stimulated, this is incapable of counteracting the excessive stimulation of the sympathetic; consequently the heart is practically uncontrolled in its tendency to speed.

The peculiar characteristics of tachycardia in Graves' disease are (1) its constancy, there being but little variation in rate between waking and sleeping hours; (2) the singular immunity to the influence of digitalis and other such drugs even in massive doses; and (3) the



relatively forcible pulse throughout the active course of the disease and almost up to the event of cardiac decompensation. The liability to acute exacerbation of heart hurry is another characteristic. This, of course, depends upon a flaring up of the entire syndrome.

I have observed that a marked slowing of the heart rate on deep expiration following deep inspiration, producing a kind of artificial sinus arrhythmia, is a sign of satisfactory amelioration of the heart hurry of Graves' disease. During the active stage of the syndrome, there is no perceptible change in heart rate on deep expiration.

Differential Diagnosis of Tachycardia.—It is a common occurrence to be confronted with an instance of heart hurry in which the diagnosis is not evident, and one is often tempted to arrive at a hasty diagnosis of thyroid hyperactivity or of Graves' disease. We must be on our guard to differentiate between this type of tachycardia and the various other forms of heart hurry commonly seen in practice.

Effort syndrome presents heart hurry, but this is paroxysmal, occurring only during physical and mental exertion, quieting down during rest and sleep. Moreover, the usual signs of typical Graves' disease are absent. It must be borne in mind that patients with so-called effort syndrome are probably pre-Graves' disease subjects. The same might be stated of many patients diagnosed as suffering with so-called "shell shock."

Congenital heart hurry, though uncommon, is met with often enough to put us on our guard. There are persons, most of them women, whose normal heart rate is somewhere between 80 and 110 or even more per minute. This is a mere peculiarity of the individual, and aside from an occasional sense of flutter or palpitation on exertion, such a person may enjoy perfect health throughout life.

Febrile tachycardia need not detain us, as the diagnosis is usually made without difficulty. It is well to remember that patients with active Graves' disease commonly present a slight rise in temperature during the afternoon and evening, but the heart frequency is entirely out of proportion to the rise in temperature.

The heart hurry due to poisoning from endogenous toxins, *i.e.*, intestinal or renal, or from exogenous substances, as caffeine, nicotine, alcohol, iodin and other drugs, presents no difficulties in diagnosis.

Hysteria, neurasthenia and the like often present a rapid heart rate, but a careful history of the case and results of physical examination soon reveal an absence of evidences of Graves' disease and the presence of existing causal factors. The heart hurry in these subjects is transitory, never occurring during sleep or during a tranquil attitude of the patient.

Organic heart disorders may present a kind of heart hurry, but the history and physical examination soon reveal the causal relationship.

Paroxysmal tachycardia occurs in paroxysms; the pulse is feeble and

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more rapid than in Graves' disease, and the cardiac discomfort is much greater. There is marked weakness and occasionally syncope. The period of tachycardia is anywhere between a few minutes or hours to a few days, rarely a week or two. In the absence of a history and physical signs of Graves' disease, the diagnosis offers no serious difficulties. Rarely, paroxysmal tachycardia may complicate the symptomatology of Graves' disease.

Incipient pulmonary tuberculosis frequently presents a rapidity of the heart action quite out of proportion to the other evidences of the disease. In fact, early phthisis and early Graves' disease present so many features in common that we must exercise extreme care in the clinical analysis of a patient in whom there seems to be some doubt as to diagnosis. There are in both conditions an increased heart rate, increased basal metabolism, often increased appetite, loss in weight, hyperidrosis, restlessness, sharpened mentality, diminished respiratory expansion, dermographia, and a rise in afternoon temperature. The discrimination between early phthisis and early Graves' disease, despite these points in common, does not offer great difficulties, for the one presents pulmonary evidences on physical and laboratory examinations, the other presents no evidences of phthisis but signs and symptoms of developing Graves' disease. It must be remembered, however, that a patient may be suffering with both diseases at the same time.

Heart hurry with simple goiter is not necessarily related, though a relationship is at times erroneously assigned. A young girl with a nontoxic goiter and a normal heart rate may enter a physician's office, and just as the doctor is about to make an examination, the heart may run off at a terrific rate. The real reason for this is the fear of the patient of a verdict of operation. Such a subject, if permitted to quiet down during 10 or 15 minutes of friendly conversation with the doctor, will be found to possess a normal pulse rate.

Tachycardia of toxic adenoma in the early stages is not quite as rapid as that of Graves' disease and not as constant, being somewhat amenable to the influence of digitalis and sleep. The patient is usually older, and as the condition progresses, the element of hypertension and arterial changes intervenes, which is readily noted. In addition, arrhythmia with or without auricular fibrillation and flutter, usually reflecting the onset of marked myocardial degeneration, is more commonly seen in toxic adenoma than in Graves' disease. The absence of physical characteristics of thyroid hyperplasia and the presence of an adenoma will render the diagnosis clear. Myocardial degeneration of toxic adenoma is frequently graver than the heart changes observed in Graves' disease. A detailed differential diagnosis between Graves' disease and toxic adenoma is mentioned elsewhere.

Tachycardia from the ingestion of thyroid extract presents many features in common with the heart hurry of toxic adenoma, as both are

due to pure hyperthyroidism. The history of the case (usually an instance of prolonged medication for obesity or for simple goiter) and a physical examination will assist diagnosis. The possibility of an onset of true Graves' disease (*in susceptible individuals*) from the ingestion of thyroid extract must be borne in mind.

Rapid heart from such conditions as the primary anemias, leukemia, debility from wasting disease, convalescence from acute infections (pneumonia, influenza, typhoid, etc.), surgical shock and hemorrhage, Addison's disease, arthritis deformans, locomotor ataxia and diseases of the central and peripheral nervous system, is discriminated from the tachycardia of Graves' disease without undue difficulty. Herrmann reports 6 cases of acute anginal attacks with a pulse rate of 170 to 250 per minute, which proved at autopsy to be due to coronary thrombosis. Though syphilis was a prominent etiological factor, only one of this series gave a positive Wassermann reaction.

The Heart Rate as an Indicator.—The basal metabolism in a patient with Graves' disease, the severity and course of the affection, and the results of treatment, are indicated by the heart rate with a precision that is dependable, as mentioned in the chapter on basal metabolism. It is only in exceptional instances that, in a patient feeling and appearing well, with a normal basal metabolism, there is a moderate heart hurry for an indefinite period of time. But this lagging evidence of the *former* syndrome yields promptly to digitalis medication.

Auricular Fibrillation.—Auricular fibrillation is very often unassociated with murmurs. The size of the heart in auricular fibrillation of Graves' disease ordinarily does not approach that of a heart in fibrillation due to the usual type of heart disease. Moreover, fibrillation in Graves' disease is more apt to be paroxysmal in occurrence. Occasionally, auricular fibrillation in Graves' disease associated with impending decompensation may give rise to such mental symptoms as periods of disorientation alternating with periods of bewilderment, confusion and excitement. I have often observed instances of visual hallucinations with persecutory delusions during which the closest relative was regarded as a designing fiend or a murderer. When not associated with advanced myocardial degeneration and evidences of decompensation, I do not regard fibrillation as of very serious import, as the cardiac rhythm is ordinarily restored within from several days to a week or two following appropriate therapeutic attention.

The Heart in Recovered Graves' Disease.—From my observations of patients discharged cured of even advanced types of Graves' disease and who have been performing their respective duties for years, I have come to the conclusion that in the great majority of instances, the restoration of the myocardium in Graves' disease is an unusually kind process and hardly interferes with the discharged patient's future. In

a considerable percentage of instances these persons enjoy unprecedented health.

However, in some belated cases in which the myocardium has undergone the changes incident to decompensation, though many become practically well, recovery from the syndrome of Graves' disease may be associated with a continuance of heart damage commonly seen following improvement from the usual organic heart disorders. So that a patient of this type cured of Graves' disease may still require attention with regard to cardiac efficiency, thus remaining to an extent an invalid throughout the rest of life. This situation, by the way, is usually traceable to a belated diagnosis and an unduly postponed institution of a rational therapeusis of the disease. Early diagnosis and the prompt institution of proper treatment will safeguard the patient's health and future. Though an internist firmly believing in nonsurgical therapy as the only rational approach to an elimination of the etiological factors of Graves' disease and the cure of the patient, I shall borrow a slogan from my good friends the surgeons and say: "Send them to us early!"

Bradycardia in Recovered Graves' Disease.—We have already mentioned a possibility of a persistence of some heart hurry in otherwise recovered patients. Undue slowness of the heart, amounting to a veritable bradycardia, may also occur after recovery from Graves' disease. This may be due to a sort of natural compensation or aftermath because of prolonged previous overwork of the heart, and may be compared to the slow heart often following other illnesses characterized during their course by prolonged heart hurry. The administration of thyroid extract, however small the dose, would be a grave error, as a relapse may be invited.

There is still another cause of slow heart occurring after the normal rate is reached; I have reference to instances of the so-called "burned out" thyroid. The patient may be observed to progress satisfactorily toward health. The weight is restored, sleep is satisfactory, tremor is gone, eyes and thyroid have returned to normal appearance, and the heart rate has reached 72 or thereabouts. But the process does not stop there. Soon the rate is observed to be further decreased, reaching 60 or less, the patient becomes unwieldy, mentality becomes dull, the skin is dry and sealy, and all other evidences of hypothyroidism supervene. Thus we are presented with a typical case of myxedema of varying degree which, fortunately, is easily controlled by thyroid extract judiciously administered.

THE BLOOD VESSELS

The symptoms of the circulatory system referable to the blood vessels resemble in many respects those observed in aortic regurgitation.

Indeed, it appears necessary at times to differentiate between the two conditions. Thus the throbbing of the superficial arteries and the capillary pulse are present in each, and even the radial pulse may appear practically identical. The throbbing vessels in Graves' disease give rise to greater subjective discomfort, however, and this symptom, ever present in the thyroid and the vessels of the neck, may aggravate the existing insomnia.

Christie calls attention to the possibility of confusing active exophthalmic goiter with aortitis. In a study of this problem, he discovered an increase in the transverse percussion dulness over the root of the aorta in many of these patients, in addition, a palpable systolic pulse and diastolic impact over the aortic area, and on several occasions a distinct tracheal tug. X-ray studies confirmed the opinion that in a number of these patients there occurs a widening of the root of the aorta. I have been able to demonstrate this in several cases in which the course is severe and prolonged. Aortic dilatation probably depends upon the general arterial relaxation beginning centrally at the heart and extending in a centrifugal fashion along the entire arterial tree. Folley directs attention to the dilatation of the abdominal aorta as well, a sign which can be demonstrated in nearly every frankly outspoken case of the disease. This throbbing and enlargement of the right ventricle are responsible for the marked epigastric pulsation commonly present in subjects of Graves' disease.

Increased vascularity of the thyroid, a pathognomonic status, may become so extreme as to lead in rare instances to pressure symptoms from the markedly swollen thyroid. Compression upon the trachea, esophagus, and the carotid sheath may lead to dyspnea, dysphagia, dysphonia, vertigo, headache, and rarely syncope and epistaxis. The thyroid, often presenting dilatation of the superficial veins, is seen to throb with each cardiac cycle. Palpation over the organ reveals a thrill and an expansile sensation resembling that of an aneurism. The grasping of the organ by the hand with moderate compression may reduce its size by the squeezing out of some of its blood. Auscultation over the organ reveals a systolic, occasionally also a diastolic murmur of harsh quality. This is pathognomonic of the hyperplastic thyroid of Graves' disease, and is present in no other types of thyroid enlargement. It must be remembered that the large vessels of the neck, too, give rise to murmurs, so that due care must be taken to discriminate these from the auscultatory signs presented by the thyroid.

Vasomotor ataxia in these patients is evidenced by (1) the capillary pulse; (2) dermographia; (3) large erythematous areas frequently present on the skin, especially the upper part of the chest beginning just below the thyroid; (4) hyperidrosis; and (5) the sensation of undue heat of the surface of the body.

The blood pressure in Graves' disease undergoes variations depending

upon (a) the condition of the myocardium and the force of the heart's action, and (b) the degree of peripheral vascular relaxation. Goodall and Rogers believe that the blood pressure in Graves' disease passes through three stages: (1) A preliminary stage of hypertension associated with the onset of the disease, and of brief duration; (2) a stage of hypotension, which is relatively long, lasting for months or years; (3) a stage of secondary hypertension which appears to be associated with "a reduction of thyroid superactivity, with consequent relative increase in that of the suprarenal" and "some secondary change in the cardio-vascular system, such as cardiac hypertrophy." In my experience, the stage of hypertension is not a constant finding. Following the usual prolonged period of subnormal blood pressure with a high pulse pressure (of approximately one to four or five years' duration), one of three things may occur: (a) amelioration of the syndrome spontaneously or through treatment with restoration of the normal blood pressure; (b) hypertension, especially in the middle aged or older, or in the presence of a history of alcoholism, nicotine poisoning, or syphilis; or (c) continued low to very low pressure depending upon cardiac decompensation and arterial relaxation. Thus the pressure may reach 100 mm. or less, with cyanosis and marked dyspnea.

Taussig points out that in Graves' disease both the systolic and pulse pressure are higher in the leg than in the arm; identical pressures in arm and leg are of some value in ruling out exophthalmic goiter.

THE BLOOD

Despite the characteristic flushed appearance of subjects of Graves' disease, there is usually a degree of secondary anemia in these patients. The toxemia, the poor respiratory expansion with consequent deficient oxygenation of the blood, the emaciation, and other factors, all conspire toward a blood impoverishment, which, because of peripheral vascular dilatation, is not evident on inspection.

However, though the general weakness of the patient may be partly due to this cause, the anemia plays a minor part in the subjective symptomatology, as blood impoverishment, except in the presence of marked vomiting, diarrhea or hemorrhage, does not constitute an essential feature of Graves' disease.

The red corpuscles in early cases may be normal in number. As the disease progresses, they may become reduced to 4,000,000 or less, with a greater diminution of hemoglobin. Thus the blood picture may approach that of chloroanemia. Holler finds that in patients with hyperthyroidism the average diameter of the erythrocytes is at the upper limits of normal or above. While there are only few polychromatophilic erythrocytes to be found with the usual methods, vitally stained corpuscles are more frequent than in healthy persons (several tenths of

1 percent.). The limits of resistance against osmotic influence are broader.

Leucopenia of varying degree is constant and to be regarded as pathognomonic of Graves' disease, especially when associated with a relative lymphocytosis. The leucocytes may be reduced to 6,000 and even 5,000 or less, with a 50 percent. diminution of polymorphoneutrophiles. The cause of these peculiar leucocyte findings is still a question. Perhaps the lymphocytosis is due to the hyperplasia of the thymus so commonly present in Graves' disease. In common with other investigators, I have observed the white blood count to be indicative of the course and prognosis of the affection; a high lymphocyte count with a moderate leucopenia is more favorable than a marked leucopenia with a low lymphocyte count.

Diminished Coagulability of the blood and *diminished fibrinogen* and *calcium content* in patients with Graves' disease are characteristic and must be remembered. The necessary precautions must be taken in case of tonsillectomy, parturition, and other events associated with the possibility of hemorrhage.

Hemorrhages from the various orifices of the body,—the nose, stomach, and bowels—at times to a dangerous degree, may occur in cases of extremely diminished viscosity of the blood coupled with marked vasomotor paralysis.

The Protein Content of the serum in these patients, when tested with the refractometer, is low, as pointed out by Deusch. These changes in viscosity of the blood and protein content of the serum may be produced in normal persons by the administration of thyroidin, thyroid extract, or thyroxin.

Hyperglycemia and other blood findings characterizing Graves' disease are discussed in the chapter on diagnostic tests.

Increased Epinephrin content in the blood in patients with Graves' disease has been demonstrated by Adler, Fraenkel and other observers. This bears out the opinion that there is a hyperfunction of the medulla of the suprarenal glands, though Elliott points out that the epinephrin content of the medulla is not increased.

Acidosis may be present in so called "acute hyperthyroidism," spontaneous or postoperative, as pointed out by Crile, Major, and others.

The Cholesterol Content of the blood is diminished, as pointed out by Weltman.

The Lipoids in the serum are diminished, as pointed out by Youchtchenko.

A potent **Depressor Substance**, believed by McCarrison to be derived from the gastro-intestinal tract, is described by Sanford and Blackford; this is said to act in many respects similar to peptone in 10 percent. solutions.

Lampa and Deutsch (quoted by McCarrison) have obtained, by

means of Abderhalden's reaction, results which appear to indicate the presence in the serum of sufferers from Graves' disease of special ferments which act on the ovaries, the thyroid and the thymus, but on no other organs. Kraus states that the serum causes dilatation of the pupil of the enucleated frog's eye.

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CHAPTER XI

NERVOUS SYMPTOMS IN EXOPHTHALMIC GOITER

THE two constant evidences of Graves' disease referable to the nervous system are *Tremor* and *Mental Changes*.

TREMOR

Tremor, rightfully one of the cardinal symptoms, was not mentioned by Graves in his description of the disease; it was Charcot and Marie who called attention to this symptom in the early history of the affection.

It is occasionally questioned whether the muscular fibrillation or trembling of the bodily musculature is the immediate cause of the increased transformation of energy characterizing Graves' disease. It appears to me that the cause of both trembling and increased metabolism is a common one, the as yet unknown cause of Graves' disease.

Though chiefly spoken of as objective, tremor is subjective as well, as most patients during the course of the disease experience a sensation of "trembling all over" which is aggravated during physical and mental activity or excitation. It is the incessant trembling of all the voluntary muscles of the body that the patient feels,—a kind of generalized clonic spasm characterizing the syndrome of the disease.

The tremor of the outstretched fingers is but the peripheral manifestation of the generalized trembling. It is an "intention" tremor, i.e., it is best elicited during voluntary muscular movement. It is a fine tremor, presenting 8 to 12 cycles per second. It may be accentuated or exaggerated by the placing of a piece of paper across and over the dorsum of the hands and outstretched fingers. In the formative stages of the disease, tremor may be seen in one finger only or in two or more fingers of one or both hands. In other words, a few fingers may appear to be free of tremor. Tremor of the fingers and hands may also be demonstrated as follows: The patient is given a tumblerful of water and requested to hold it a moment, then carry it slowly to the mouth. As the glass approaches the lips, it will begin to vibrate, and if full, some of the water will be spilled. In examining for tremor of the toes, the method of hyperextending them is employed as for the fingers.

Tremor or twitching of the tendons at the wrist is observed when the pulse is taken. In fact, all the voluntary muscles of the body

vibrate at the same rate as is observed in the outstretched fingers. For instance, the examiner on grasping the muscles of the patient's shoulders, thigh, or those of the arm or forearm will be impressed with the fact that *tremor is universally present*.

During recent years I have found the foot and leg tremor to be of service in demonstrating the extreme state of vibration or trembling characterizing the syndrome of this disease. I believe that I am the first to call attention to this sign. The patient is told to cross the legs; the upper leg is then extended straight ahead, the thigh still resting upon the lower one. The entire leg, but especially the foot, will present the same tremor as is observed in the outstretched fingers, but in magnified degree.

Tremor is one of the earliest expressions of Graves' disease. This symptom, associated with a constant afebrile tachycardia in a patient complaining of functional digestive disorders or of nervousness, should

*This is an only picture
we can find. The one
on other paper is
one. It was taken, b
years ago.*

FIG. 68.—Specimen of handwriting in a case of severe Graves' disease with typical tremor.

arouse at least a strong suspicion of the development or existence of Graves' disease.

Tremor of the protruded tongue, and tremor of the eyelids (Rosenbach's sign) are also observed in Graves' disease.

Differential Diagnosis of Tremor.—The tremor of Graves' disease must be differentiated from that of certain other affections. For instance, in *hyperthyroidism* or *toxic adenoma* tremor is not constant, less rhythmical and coarser than that of Graves' disease. In *hysteria*, the tremor is fine and rapid or slow and coarse, varying in rhythm, frequency and regularity; it appears and disappears, depending upon the whims and moods of the patient; it is absent during sleep. In *neurasthenia* the tremor resembles that of hysteria, excepting that it is less constant and more apt to be regular and rhythmical, and is quite amenable to treatment. The tremor of *emotional excitement* or after violent or long continued *exercise* is transient.

The various *intoxications* due to tobacco, tea, coffee, alcohol, lead, arsenic, and in morphin and cocaine habitués, are characterized at first

by "intention" tremors, but as time goes on they become constant, and with the advance of the toxic process, muscular coördination becomes progressively more difficult.

Paralysis agitans presents a tremor distinguishable from all others in that it is of the slow, "bread crumbling" or "pill rolling" variety, ceasing during voluntary effort. The slow, monotonous speech, blank countenance, peculiar gait and posture on walking render the diagnosis clear. Tremor of *senility* is rapid and at first "intention" in type, becoming constant as age advances; it begins in the hands, gradually extending to the muscles of the neck and the rest of the body. The tremor occasionally *inherited* through a long line of descendants resembles the senile tremor. Multiple *sclerosis* presents an "intention" tremor that is slow and irregular. The movements characterizing *chorea* are not tremors but merely sudden, nonpurposive, incoöordinated movements of various groups of muscles, which movements cease during voluntary effort, attention and sleep. Any *organic abnormality of the nervous system* is apt to give rise to a tremor of varying type or degree. All tremors must be judged on the merits of the case; the clinician who has a fair knowledge of diseases of the nervous system on the one hand and is well versed in the various manifestations of Graves' disease on the other will not be troubled by the pitfalls which stand in the way of the superficial observer.

In patients with an extremely excitable heart during the course of Graves' disease, I have noticed a rhythmical nodding of the head and occasionally of the whole body, the rate corresponding to the number of cardiac cycles per minute. Though this may in a very broad sense be considered as a tremor of the head and body, strictly speaking it is not so, since it is not of nervous, but of cardiac origin. The heart beating at the rate of from 110 to 160 per minute labors so strenuously that it soon becomes enormously hypertrophied, so that this organ, acting as a huge, excited pump within the chest, takes with it, as it were, the head, shoulders, body, and all, during each contraction.

MENTAL CHANGES

Mental changes varying from a mere inconspicuous change in temperament and disposition to an actual grave major psychosis are commonly seen in Graves' disease. Occasionally, restlessness, impatience, and emotional outbursts may precede by weeks or months any definite evidences of Graves' disease.

Emotionalism and a departure from the usual behavior are constantly present, though in patients with an inherently strong will power outward manifestations may be lacking. Ordinarily, the patient, quite conscious of these changes, will venture to complain to the doctor of "nervousness." When pressed for a definition of the symptom, the

patient will say: "I am easily excited," or "The least thing upsets me," or "I am jumpy," or "I feel trembly all over," or at times the frank expression: "I don't seem to be able to get along with any one at home." The average patient is easily excited; the slightest noise, a sudden call, a slight peal of thunder, and the exophthalmos is markedly accentuated, the heart thumps away at a terrific rate, and the features become more distressed and anxious than ever. They are easily aroused to the extreme of almost any emotion: fright, anxiety, terror, suspicion, anger, may alternate with surprising rapidity and upon the most trivial provocation. Tears, laughter, pensiveness, unnatural gayety and mental activity alternate with irrelevant order and frequency. There is often a peculiar sense of bewilderment of which the patient may actually complain,—a sense of unreality or strangeness, a lacking sense of orientation suddenly thrust upon the mental structure of the patient by the drive or quickening influence of the etiological toxins of Graves' disease. Inherent mental flaws are brought to the surface and so magnified by the disease as to virtually crowd out the rational experiences of previous selfhood. Thus many of these patients seem to experience an existence in another mental world which suddenly looms upon their mental horizon. In obtaining the history of a male patient suffering with early exophthalmic goiter his wife made the following significant remarks: "George has not been himself the last several weeks—I can't make him out. He acts queerly—different from his usual behavior. He does things he never did before; he says things I least expect of him. He becomes impatient and excited for no reason and cries like a baby without the least cause. I try to be as good as possible to him, but I can't make him out. I don't understand him any more. Do you think he'll lose his mind, doctor, or is he just nervous?" This is a common situation, whether it be in male or female, married or single. The relatives and friends cannot "make the patient out" or, to be more lucid, there is a diminished or an absence of "understanding" between the patient and those about him.

Frequently there is an evident desire to display intellectual aptitudes, and other egoistic tendencies may be noted. One of my patients, a young professional man, after expatiating with me on Kant's "Critique of Pure Reason" for about ten seconds, suddenly shifted to the subject of palmistry, then, like a flash, to metaphysics, and after a few seconds' remarks on musical composers, suddenly asked: "Doctor, do you think study would hurt me?" "Study of what?" I inquired. "Law," he replied. "Law!" I said, in astonishment. "Why, if you were a lawyer, you would lose every case; it's too exciting for you." "That's why I like it," he retorted; "I like mental excitement." I quickly changed the subject to the matter of his treatment, and handed him over to the care of his nurse.

The patients' visit to the doctor's office is replete with trifling but

interesting incidents characteristic of these patients. Speech is hasty and often somewhat slurred, voluntary movements such as sitting down, rising, turning about to respond to a question,—all these are done in a sudden, precipitous, jerky fashion. On entering the office, the extremely toxic patient comes "breezing" in, and though smiling, the news (in a recent case of mine) that ice skating and tennis must not be indulged in for a year or two brings big tears to the surface with remarkable celerity. Even while seated and listening to orders in treatment, the patient is not still, jerking now this, now that foot, hand or shoulder, the motions resembling in a way the purposeless movements of chorea. There is, of the mind, too, a "veritable chorea" of activity.

Talkativeness and emotionalism are not altogether objectively perceived. Many of my patients have made such remarks as the following, indicating a consciousness of aberrations in behavior: "Doctor, I talk too much, but I cannot restrain myself." Again, "I cry over nothing;—I feel ashamed of myself, but I have no control over my emotions."

At times, in advanced Graves' disease, instead of evincing an overly alert hyperactive demeanor, the reverse is seen. The patient is morose, moody, and melancholy, fretting the time away. This may be due to the results of *over-stimulation*, with consequent depression of the brain cells by the toxemia. The patient is physically and mentally depressed and apathetic. The mind, left to itself, soon reverts to such pathways as anxiety, apprehension, phobias, obsessions, persecutory delusions, unwarranted suspicions, and, rarely, hallucinations.

The emaciation, the staring eyes, and the departure from the normal of the subject's manners, all conspire to deserve for the patient the title "queer" from those about him. This patient, though formerly capable of sustained physical and mental effort, is now quite different. The sharpened intellect and drive of determination to accomplish seen in such a subject remind one of the spur to action from the use of moderately large doses of caffein; but in Graves' disease, the individual tires of the matter in hand more easily. He is enthusiastic, intense, and eager for brief periods only. Tastes and desires vacillate with unusual rapidity. The marked lack of perseverance, shiftlessness, a tendency to hop from relevant to irrelevant thoughts, expressions, and actions characterize the day's events. Excitability, restlessness, agitation, and depression are soon common attributes of thought and action. When evening comes, sleep is not a cheerful prospect, and when the patient retires, attempts at rest are unsuccessful. The insomnia and tossing about in bed, the sweating and throbbing of the heart, especially when lying on the left side, make the break of day an eager anticipation. The patient, though glad to leave bed, arises in the morning feeling "all in"—tired, weary, gloomy, irritable, and

totally unfit for work or society. Thus the next day and night are spent in similar fashion, and so on through weeks and months. Is it any wonder that in many instances the mind sooner or later gives way under this strain, with resulting mania or dementia?

Typical evidences of *neurasthenia* and *hysteria* are commonly seen in exophthalmic goiter. *Neurasthenia*, *hysteria*, or *hysteroneurasthenia* usually (a) precede the syndrome by some weeks or months, and may mask the true diagnosis; (b) they may appear concomitantly with one or more cardinal signs of the syndrome; (c) they may occur weeks or months after the diagnosis of Graves' disease has been definitely made.

Psychoses in Graves' Disease are unfortunately observed in a goodly percentage of patients. There is no strict dividing line between sanity and insanity, since there is no adequate definition of these terms. However, when a patient behaves so differently from his fellows that he is thought to be dangerous to himself and to society, the abstract conception of what is recognized as insanity is reached, and the necessary restraint and treatment are instituted.

When it is recalled that in the great majority of patients the exciting cause of Graves' disease is a variety of psychic trauma or acute mental or emotional strain, it is readily recognized that mental symptoms play an important, occasionally a dominating rôle throughout the course of the disease. The mental manifestations vary with the nature of the pre-existing psychopathic make-up, and often with the age, sex, and culture of the individual. Upon the previous mental structure of the patient depends the degree of vulnerability of the psychic centres to dominating mental symptoms instigated by Graves' disease. Many subjects of the disease have approached the arbitrary threshold of insanity in varying degree, and may suddenly step into this category at any time.

The bibliography on the subject of the relationship of insanity to Graves' disease is very ample. The manic-depressive type of psychosis, dementia, melancholia, dementia praecox, and other types of insanity are seen during the course of the disease. It must also be borne in mind that in occasional instances Graves' disease and insanity may coexist and are not necessarily causally related, though in most instances the Graves' syndrome is the basis of the complex clinical picture. Biggs calls attention to the frequency of the association of insanity with hyperthyroidism with or without Graves' disease, in which the Wassermann is positive, though the history and physical examination are negative for syphilis. His series of cases was characterized by wild delusions and irritability which sometimes developed into acute excitement. The prevailing mental tone associated with the disease was fear and apprehension, frequently associated with hallucinations of hearing and vision; voices were heard saying disagreeable

things, and with these hallucinations occurred anxious and agitated states. Buckley believes that Graves' disease and insanity may exist in different members of the same family. He calls attention to a woman with Graves' disease as having a daughter who is a cretin idiot. Packard analyzed a series of 82 cases of mental disorder associated with thyroid malfunction,—20 men and 62 women. In 6 percent. there was a definite heredity of Graves' disease. Wimmer emphasizes the fact that the most common form of insanity in Graves' disease is the manic-depressive type. Philips, in an examination of 200 cases of insanity, discovered that 24 had thyroid enlargement; 17 of these patients suffered with manic-depressive insanity or from the melancholia of involution. Of the remaining 7, 4 were cases of dementia *præcox* and 3 were cases of paranoia. In my own experiences with a large series of cases of Graves' disease, I find that approximately 3 percent. are actually suffering with frank manifestations of a complicating insanity requiring treatment as such. The following illustrative examples are typical:

Case 1. A married woman of 32, referred for treatment of exophthalmic goiter, presented the following mental symptoms: Complete mental apathy and helplessness, total absence of familial responsibility, an attitude of quarrelsomeness and "upishness," and an implied claim for a maximum



FIG. 69.—Patient mentioned in case 1.

amount of sympathy and attention, which was especially evidenced by the necessity on the part of medical attendants and relatives to repeat a question several times before a response was forthcoming from the patient. The patient's hearing was entirely normal, for she so informed me, and responses were exceedingly prompt following remarks which she resented or which

pleased her. In matters of every day routine, there was a total jelly-fish-like attitude. Associated with these features, there was complete stubbornness and disobedience to instructions in treatment; reasoning with her was a waste of time, and all she would say in response to urgings for better coöperation was, "Well, doctor, I have done my best," despite the fact that she did her worst. In addition, she was possessed of an obsession to the effect that her husband and some one else whose name she did not mention had done her an irreparable harm sometime ago, which was responsible for her plight.

Case 2. A male, aged 42, developed a rather progressive form of Graves' disease following shortly after business failure. From the chaste, respectable head of his household, his mental manifestations focused themselves upon the sexual impulses. Continuous ungratified desire associated with priapism

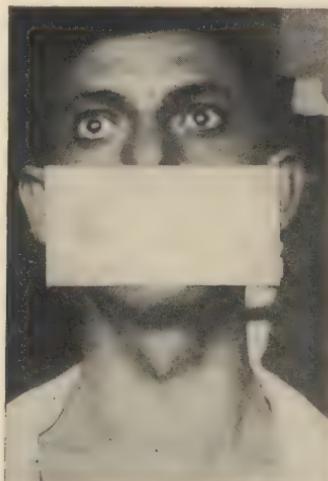


FIG. 70.—Patient mentioned in case 2.

led to a complete eradication of moral sense and responsibility. So far did the situation progress that his wife and others who knew him soon realized that he was having sexual relations with his former women employees. Associated with this sexual irrationality, his general behavior became such that he was rapidly approaching a dangerous major psychosis.

Case 3. A married woman of 47 who had been unsuccessfully operated upon twice up to within three years before being referred to me progressed most satisfactorily in every respect under nonsurgical management, and it was thought that recovery was approaching. At this point, one day as she was preparing to go shopping, she fell down a flight of stairs and struck her head, which mishap rendered her unconscious for a few minutes. An exacerbation followed in which there was at first extreme weakness, complete insomnia, incoherent speech, auditory and visual hallucinations, and persecutory delusions in which her husband was regarded as a designing fiend who must be kept away from her. The typical evidences of exophthalmic goiter

were also aggravated but not to any serious extent. The mental status becoming worse, with inability to keep the patient quiet in bed, she was sent to an asylum. There her condition in the course of a few weeks became so alarming that it was thought she was moribund. Her relatives and friends were unrecognized, and periods of mania alternated with periods of exhaustion, with complete insomnia pervading the day and night. The destructive tendencies of the patient were such that some days she would tear up six or more bed-sheets, despite the restraining efforts of day and night nurses who were constantly with her. Delusions, illusions, and hallucinations of all



FIG. 71.—Patient mentioned in case 3.

sorts were present. Following her periods of quiescence because of exhaustion, her maniacal activities were associated with howls and shrieks alternating with weird singing of which the other inmates of the asylum complained. Food, drink, and medication were practically impossible to administer, and force was required to introduce some fluids into the body, most often by rectum. From a woman formerly weighing 140 pounds she was reduced to almost a skeleton, and the end was expected at any moment. After hovering between life and death for 12 or 13 weeks, she suddenly rallied, her mind became clear, and in the course of a brief while the patient made a complete recovery.

Did space permit, many more instances of insanity in Graves' disease could be described to indicate that the syndrome involves the central nervous system quite as prominently as any other part of the economy. I have found that patients who have gone through one or more operations upon the thyroid gland are more prone to the development of insanity than unoperated patients. The probable reason for this is that the organ, deprived of some of its substance and detoxicating function through thyroidectomy, is incapable of immunizing the body as well as formerly, the result of which is an overwhelming of the central nervous system with the etiological toxins.

During the course of acute Graves' disease, or the so-called acute hyperthyroidism often seen after thyroidectomy, active delirium and

maniacal excitement are common. This is associated with high fever, tumultuous heart action, extreme nausea, retching, vomiting, diarrhea, very rapid emaciation, and often collapse of all the vital forces, stupor and death.

Finally, I cannot emphasize too strongly the vital importance of an early diagnosis as a condition of prompt recovery of the patient. Presented with a patient with vague mental symptoms, early exophthalmic goiter must always be regarded as a possibility even in the absence of enlarged thyroid and exophthalmos. Change of temperament and of disposition, an unusual quickening of cerebration with corresponding impairment of perseverance of purpose, a reduction in the threshold of emotional response, with emotivity,—these, associated with the characteristic intention tremor and an unaccountable, afebrile heart hurry, are very often significant of developing Graves' disease.

Miscellaneous Nervous Phenomena.—*Insomnia* is almost the rule in Graves' disease and differs in intensity with the exigencies of the case. The causes of sleeplessness are usually a combination of the following: (1) Throbbing vessels of the neck, thyroid and ears; (2) throbbing and palpitation of the heart; (3) trembling; (4) hyperhidrosis; (5) a sensation of heat; (6) mental excitation; (7) itching of the skin; (8) nocturia; (9) neuritis; and (10) occasional diarrhea. All of these rob the subject of the night's rest and cause the patient to dread the close of day. Thus a patient is apt to arise more fatigued than on retiring. Impaired, unrefreshing sleep is an early symptom; complete insomnia characterizes the frank syndrome; on the other hand, the tendency to sound, refreshing sleep is an excellent evidence of successful treatment and a beginning restoration to health.

Neuritis is commonly observed as a complication in Graves' disease. It usually affects the nerves of an arm or leg, usually one arm, extending from the shoulder downward to the tips of the fingers. The pain may become so severe as to dominate the entire situation, so that a patient hitherto progressing satisfactorily may suddenly regress dangerously toward the primary status through the incessant torture and consequent insomnia.

Pains in various parts of the body are commonly experienced, resembling in character those occurring in diabetes mellitus. A feeling of weakness in the knees and calves of the legs is often early and distressing. These pains often appear rheumatic in nature, but care must be exercised in making deductions.

Headache is not common. When it occurs, it is usually frontal, but may vary. At times attacks of typical *migraine* of varying intensity and duration may occur.

Epilepsy and *Chorea* are occasionally seen in subjects of Graves' disease; these are probably not causally related, but incidental to the syndrome of the affection.

Reflexes are usually exaggerated, for the threshold of nervous response is lessened in Graves' disease. In the unusually depressed patient, however, the reflexes may be normal or even somewhat sub-normal.

Rarely, there are observed associated with Graves' disease such affections as *Parkinson's disease*, *acromegaly*, *tetany*, *myasthenia gravis*, *encephalitis lethargica*, *paresis*, and other conditions of the nervous system.

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CHAPTER XII

THE THYROID GLAND IN EXOPHTHALMIC GOITER

THE thyroid gland is usually enlarged to goiter formation in Graves' disease, but this is by no means a cardinal sign. There are many patients who present a questionable swelling of the organ, others whose thyroid becomes large late in the disease, and still others who never at any time present goiter. It must be emphasized, however, that though a thyroid in Graves' disease may appear normal on *inspection*, the gland is nearly always *unduly palpable*.

In short-necked people, it may be difficult to ascertain the size of the thyroid, because the organ may be situated somewhat retrosternally. If the patient is made to extend the neck and ordered to swallow, the gland may be felt to ascend above the suprasternal notch and can be palpated with comparative ease.

Rarely, an accessory thyroid structure, anomalously situated in the thorax, at the base of the tongue or elsewhere, may undergo hyperplasia during the course of Graves' disease, and thus explain the apparently normal neck presented by the patient. Of course, in most instances of this sort, the diagnosis should be confirmed by the roentgenologist. In these unusual cases the patient may complain of such pressure symptoms as alteration of voice, choking sensations, or cough.

In the average case of exophthalmic goiter, enlargement of the thyroid occurs. Some time after a period of nervousness, palpitation, and loss in weight,—perhaps several weeks or months,—the male patient begins to realize that there is something wrong with the front of the neck, for collars usually worn, size 15 for instance, have become uncomfortably tight, and size 15½ is just about right. A woman will begin to realize that her "throat" is unusually full despite a recent loss in weight, and that there is a sensation of a lump moving up and down during deglutition. Soon it is discovered that there is a real bulging in the front of the neck, and manipulations over the thyroid give rise to a feeling of uneasiness and tenderness. During all this time, the other evidences—eye signs, heart manifestations, nervousness, trembling, loss in weight, and general weakness are intensified, and the patient seeks medical advice. In most instances it is the advent of a large neck that brings the patient to the doctor—often dangerously late in the course of the disease.

Physical Examination of the Thyroid.—Physical examination of

the thyroid is of exceeding importance—quite as much as examination of the eyes, heart or nervous system, for inspection, palpation, and auscultation yield information of value from both a diagnostic and prognostic viewpoint. In fully 90 percent. of instances at least, the internist well trained in this work should be capable of diagnosing a case of Graves' disease by physical findings of the thyroid alone, with the remainder of the patient—above and below the neck—screened off. Even the heart rate, regularity and rhythm may be ascertained over the thyroid. There is no other thyroid enlargement presenting physical signs approaching those in Graves' disease. On the other hand, the inexperienced examiner who fails to apply his senses directly over the thyroid gland is one who will often err in diagnosis, as he has missed certain pathognomonic points.

Inspection.—The size of the thyroid on inspection of a patient with exophthalmic goiter varies from an apparently normal thyroid to one of rather large proportion, never, however, assuming the enormous size frequently attained by large encapsulated tumors of the thyroid. The average patient with Graves' disease presenting enlargement of the thyroid has a smaller neck than the average patient presenting a simple goiter. The shape of the goiter in Graves' disease is usually symmetrical and the swelling diffuse, conforming to the area of the normal thyroid. Uncommonly one portion of the gland is involved, the remainder appearing normal. Again, one lobe or the isthmus alone may be larger than the remainder of the gland. Usually, the mass is evenly distributed, with a slight tendency toward greater swelling of the right lobe than elsewhere. This is also observed during recovery from the disease when the gland is seen to regain its size throughout, excepting the right lobe, which remains larger than normal for a month or two longer. Rarely, the goiter may appear nodular. Ordinarily, it is smooth and boggy in appearance, as distinguished from all other types of goiter which are apt to present almost any shape or form and any kind of irregularity of contour. Further inspection reveals in many instances the presence of dilated veins coursing beneath the skin over the organ. The skin may appear of purplish hue. The mass moves up and down with the movements of the larynx and with deglutition. The skin moves freely over it, unless the goiter is of unusual size, when the skin over it may be tense. An inconspicuous enlargement may be brought into bold relief by having the patient hyperextend the neck and swallow, when it may be seen and felt by the examiner. Throbbing of the hyperplastic thyroid is seen when the enlargement is exceptionally vascular. The throbbing corresponds to the cardiac cycles, resembling in some respects the heaving of an aneurism. The arteries of the neck are commonly seen to participate in the throbbing of the thyroid, and in severe cases even the head may nod synchronously with the throbbing.

Palpation confirms inspection regarding size, shape, symmetry, mobility, and throbbing. The gland is moderately soft and yielding, but if it is in the process of rapid growth at the time of examination, or if fibroid changes have occurred, resistance to the palpating fingers is increased. Rough handling or deep palpation of the thyroid elicits tenderness. A thrill comparable to that observed over the heart in mitral stenosis or aortic regurgitation is elicited in well-advanced cases. On grasping the thyroid with moderate compression, the examiner usually succeeds in expelling a quantity of the blood from the mass in much the same way as one expresses water from a distended sponge, thus reducing its size. This cannot be done with other forms of goiter.

Auscultation.—The essential characteristic of the hyperplastic thyroid of Graves' disease is its vascularity. This has already been intimated by the throbbing of the mass and by the ability to compress some of its vascular contents by grasping with the hand as has been mentioned. The thrill, too, is confirmatory. The most important evidence of vascularity is the bruit, which is pathognomonic. The murmur is systolic, often also diastolic in time, rather loud and at times uncomfortably harsh to the ear, simulating that heard over an aneurism.

The bruit of the hyperplastic thyroid must be elicited with care, lest false deductions be made. A bruit may be gotten over almost any neck, if the bowl of the stethoscope is placed over or near the large vessels. Auscultation must be practiced strictly over the thyroid area, not outside of it. Murmurs over the carotids are systolic and of the same duration as the cardiac systole, and are rather soft in character. The murmur over the vascular thyroid is of greater duration than the cardiac systole; it may be systolic and diastolic and is harsher in quality.¹

To summarize the characteristics of the thyroid swelling observable in Graves' disease, we might state that (1) the swelling is essentially hyperplastic and vascular; (2) it is symmetrical; (3) it throbs; (4) it is most often capable of being reduced in size by pressure; (5) there is usually a thrill and bruit.

¹ Depending upon the increase in the size of the blood vessels in and about the thyroid gland during its stage of active hyperplasia, H. H. Lissner (*Endocrinology*, 1923, I, 431) describes a bruit which he regards as a sign of hyperthyroidism. This bruit is unlike the murmur over the gland and is heard just behind and below the sterno-clavicular junction, about 1 to 2 cm. either to the right or left, corresponding to the position of the inferior thyroid artery. The thyroid need not be enlarged as a condition of the existence of this sign. The bruit is hissing or siren-like in character as differentiated from the whirring or water-wheel churning sound heard over the gland itself. The sound is most often heard over the right side, is increased by deep inspiration, is systolic in time, is inconstant, and is apparently dependent upon the accelerated heart action for its production. Other probable factors are the increase in the rate of the blood stream and arterial changes.

These characteristics, to repeat, are not present in any other form of thyroid enlargement, and are sufficient in themselves to typify Graves' disease. We might make this abstract generalization regarding the difference between the goiter of Graves' disease and simple goiter: In exophthalmic goiter the average patient complains least of all of symptoms referable to the neck, the main complaints pertaining to the circulatory, nervous, and digestive systems;—in fact, almost every portion of the body but the neck is complained of. In contradistinction to this, the average patient with simple goiter will complain of the neck only; the remainder of the body presents no subjective or objective symptomatology.

CHAPTER XIII

THE EYES IN EXOPHTHALMIC GOITER

NEXT in importance to a consideration of the thyroid gland, the eye symptoms deserve our attention in the study of Graves' disease.

Exophthalmos.—It is the bulging forward of the eyeballs characterizing both fright and Graves' disease that gave rise to the term exophthalmic goiter, and led a large percentage of observers, both orthodox and modern, to attribute the disease to shock to the emotions. In 1882, Claude Bernard confirmed the observations made in 1873—namely, that irritation of the sympathetic produced exophthalmos, and that section of the ganglion overcame the ocular protrusion. In accordance with Trousseau's theory that exophthalmic goiter is due to a disturbance of the cervical sympathetic, Jaboulay, and later Jonnesco and others, operated on the sympathetic with a view to curing the syndrome. Although the exophthalmos was reduced to a marked degree in many cases, the operation is now practically discarded as impracticable.

Exophthalmos occurs sooner or later in from 65 to 85 percent. of subjects of Graves' disease. It may occur early and suddenly in instances where extreme fright or terror is responsible for the syndrome, as, for example, the explosion of a bomb or participation in an automobile accident. Ordinarily, this symptom is gradual in coming, occurring months after the onset of the cardiac and nervous phenomena. I do not concur with Claiborne who contends that exophthalmos is the first symptom to occur in exophthalmic goiter. Many subjects of this disease never present exophthalmos. Proptosis is, in the vast majority of instances, the first *eye sign* to be observed, if the patient is to present eye manifestations at all. Occasionally, an inconstant von Graefe's sign will precede the appearance of proptosis, and, more rarely, the "hitch sign" of the upper lid may be observed. Though occasionally a patient will apply for treatment with exophthalmos as the only complaint, a careful examination at this time will reveal the presence of heart hurry, tremor, dermographia, and other evidences of Graves' disease, which have developed prior to the exophthalmos, and which have occurred in such an insidious fashion as to have escaped the patient's attention.

The earliest occurrence of exophthalmos is seen when, following a sudden intense emotional strain, there is an acute onset of the disease.

For example, a man of forty-five, while in an automobile, suddenly drove into a ditch in the road, wrecking the front part of his car. He was thrown forward with extreme violence, and when he was taken home, the family noticed that his eyes were protruding, his neck swollen, his skin covered with profuse perspiration, and all other evidences of Graves' disease were present. Another patient, a girl of eighteen, while enjoying herself in an amusement park, was thrown from a carousel. She was taken home in a condition of hysteria, and within a day or two, exophthalmos and all the other evidences of Graves' disease developed. Many such examples might be cited.

In the average case there is observed at first an unusual stare of the eyes during active attention and conversation, and this, plus the moodiness and nervousness, causes the family to suspect that the subject is becoming "queer." The stare soon becomes permanent and more marked than ever, until in course of time the patient's relatives and friends become somewhat alarmed about his expression.

The degree of exophthalmos varies with the severity and the duration of the disease, and though it may not fluctuate to the extent of the vacillations seen in the enlarged thyroid, yet it is seen to vary temporarily and become exaggerated during physical and mental excitement, exertion, active attention, and menstruation. These factors may increase the protrusion of the eyes until they seem ready to "pop out." Indeed, in rare cases there is no discernible cause for a rather malignant progress of exophthalmos in an otherwise moderate attack of Graves' disease, the eyes continuing to bulge more and more forward, with very sad consequences. I have seen a case in which, after the use of thyroid extract as a therapeutic measure, there resulted a virulent infection of the eyeballs from ulceration through exposure, so that a double enucleation became necessary to save the patient's life. In several cases of mine (which have now completely recovered) the patients were obliged to place small pads of cloth over their eyes at bedtime for protection from exposure.

Ordinarily, exophthalmos is not severe enough to occasion serious damage to the ocular mechanism. In most instances, the conjunctiva is somewhat congested, occasioning little or no discomfort to the patient. In instances where the eyes bulge markedly, closing of the eyelids is accomplished with difficulty. Such patients commonly experience a burning sensation in the eyeballs, early fatigue of vision, excessive dryness or excessive moisture of the conjunctiva, and a varying grade of chronic conjunctivitis. In a small percentage of patients, the exophthalmos is extreme, reaching the point at which the eyelids are incapable of coaptation, so that the patient cannot close the lids on retiring. It is then that serious trouble may begin, for the eyeballs cannot long withstand the absence of the protection offered them by the lids. In some cases, a mere thirty-second of an inch is lacking to

EXOPHTHALMOS AND AGE OF PATIENT

AGE OF PATIENTS	TOTAL									
	Under 10 years	10 to 15 years	15 to 20 years	20 to 30 years	30 to 40 years	40 to 50 years	50 to 60 years	60 to 70 years	70 to 75 years	75 years
No exophthalmos	38	80	147	54	42	20	10	4	400	
Exophthalmos on attention only	5	1	1	1	1	1	1	1	1	39 (94%)
Slight exophthalmos	3	3	12	10	6	2	1	..	46 (11½%)	
Moderate exophthalmos	12	18	26	12	7	4	1	1	62 (15½%)	
Marked exophthalmos	5	15	30	10	7	6	2	2	92 (23%)	
Extreme exophthalmos	2	2	16	3	2	1	1	1	28 (7%)	
Unequal exophthalmos (greater in right eye)	3	2	3	3	1	1	1	1	13 (3½%)	
Unequal exophthalmos (greater in left eye)	2	4	2	5	2	1	1	1	12 (3%)	
Unilateral exophthalmos (right eye only)	4	2	4	1	3	1	1	1	17 (4½%)	
Unilateral exophthalmos (left eye only)	2	2	6	1	1	1	1	1	14 (3½%)	

form complete coaptation, while in others the eyes remain permanently open night and day, the lids being incapable of closing to within half an inch or more. This frequently leads to corneal ulcers and opacities, with varying degrees of impairment of vision. Unprotected eyeballs are occasionally a causal factor in the insomnia common to patients with Graves' disease.

Usually the moderate or marked exophthalmos in these patients remains a more or less constant factor with little variation in degree until the syndrome is terminated. In a not inconsiderable percentage of patients in whom the course of the disease was protracted to eight, ten, or more years, the exophthalmos may become less severe, with an accompanying edema of the upper and lower lids. This edema may be local, due to chronic congestion of the orbital tissues; occasionally it may be a kind of myxedematous infiltration or it may be an evidence of circulatory decompensation.

Exophthalmos and Age of the Patient.—In a study of the exophthalmos in 400 recently reported patients¹ under my observation, the preceding data are of interest with regard to the relation of this sign to the age of the patient.

No relationship seems to exist between the age of the patient and the probable development of exophthalmos during the course of Graves' disease. With regard to the degree of exophthalmos, it might be said that in very young subjects of Graves' disease (under 10 years of age), there is apt to be slight or moderate exophthalmos. As we approach puberty, adolescence, and go on to patients in early adult life, bulging of the eyes becomes more prominent. Past the age of 40, the tendency towards moderation of exophthalmos becomes manifest.

As can be seen from the above data, exophthalmos is occasionally more marked on one side than on the other, or it may occur on one side only. In rare instances it may be unilateral for a long time, and finally the other eye may become affected to an equal or unequal degree.

Exophthalmos and Goiter Incidence.—The tendency toward goiter formation seems greater in patients with exophthalmos than in those without; perhaps the reverse may also be stated, i.e., the tendency to exophthalmos is greater in those with thyroid swelling than in those whose thyroid is normal in size.

There seems to be no relationship between unilateral or asymmetric exophthalmos and unilateral thyroid enlargement. A right-sided exophthalmos, or a right-sided accentuation of exophthalmos, may exist just as often with a symmetric thyroid enlargement as with an enlargement of the right or of the left lobe only of the organ. In other words,

¹ These tables and data on the clinical aspects of exophthalmos are largely quoted from an article of mine in the *American Journal of Ophthalmology*, 1922, 5, 609-622.

RELATIONSHIP OF EXOPHTHALMOS TO GOITER IN GRAVES' DISEASE

	NO. EXOPHTHALMOS PRESENT	EXOPHTHALMOS PRESENT	TOTAL
No thyroid enlargement.....	22 (5.5%)	56 (14%)	78 (19.5%)
Slight thyroid enlargement.....	4 (1%)	84 (21%)	88 (22%)
Moderate thyroid enlargement...	8 (2%)	103 (25.75%)	111 (27.75%)
Marked thyroid enlargement....	5 (1.25%)	98 (24.5%)	103 (25.75%)
Extreme thyroid enlargement....	..	20 (5%)	20 (5%)
Totals	39 (9.75%)	361 (90.25%)	400 (100%)

the symmetry or asymmetry of the exophthalmos seems to bear no relation to the symmetry or asymmetry of the thyroid enlargement.

Exophthalmos and Severity of the Disease.—The degree of exophthalmos bears no definite relation to the severity of the syndrome of the disease. While we often observe a more severe course of the disease in patients with marked exophthalmos than in those with little or no bulging of the eyes, exceptions to this are so often seen, that one should hesitate to state percentages or suggest rules in this regard. Very severe instances of the disease with auricular fibrillation and with cardiac decompensation are often seen in patients who never, at any time, present either exophthalmos or goiter. In fact, so often is this observed, that one is tempted to regard this class of patient as suffering with a definite type of the disease. The basal metabolism frequently appears much higher in a patient with slight or no exophthalmos than in one whose eyes seem to pop out of their orbits. In general, it may be said that a patient with slight or moderate exophthalmos and thyroid swelling is usually a subject of Graves' disease of average severity. Exceptions *pro* and *con* are numerous.

Exophthalmos and Sex.—The sex incidence in this series of cases differs somewhat from statistics of other observers. Of the 400 cases tabulated above, 136, or 34 percent., occurred in males. Of the 39 patients without exophthalmos, 18 were males,—13.2 percent. of the total number of male patients, and 21 were females,—7.9 percent. of the total number of female patients. This would indicate that during the course of Graves' disease, females are more apt to develop exophthalmos than males.

Exophthalmos and Toxic Adenoma.—Toxic adenoma is to be dif-

¹ Though exophthalmos is absent in toxic adenoma, one may at times observe a stare in these patients, without the von Graefe and other eye signs commonly seen in Graves' disease. This is not due to the hyperthyroidism, but to the impaired circulation to the head and eyes from pressure upon the cervical blood vessels by the adenoma, if the tumor be large. Staring eyes may also be observed without thyrotoxemia in instances of pressure due to intrathoracic goiters giving rise to the so-called "mechanical goiter heart," in which dyspnea is a distressing feature.

ferentiated from exophthalmic goiter by the absence in the former of exophthalmos and other eye signs characterizing the latter. The other clinical differences between toxic adenoma and exophthalmic goiter are mentioned in the chapter on the diagnosis of exophthalmic goiter. In this connection we must bear in mind that a person with a simple or nontoxic goiter may develop exophthalmic goiter with or without exophthalmos quite as readily as any one else. Presented with a patient who reveals all the signs and symptoms of Graves' disease, but in whom there is an adenoma over the thyroid, we must not conclude that we are dealing with a case of toxic adenoma with exophthalmos. This patient, on final analysis, may be suffering with a hyperplasia of the formerly normal thyroid tissue behind the adenoma, associated with the generalized neuro-endocrine dysfunction characterizing Graves' disease. In such an event, the presence of the adenoma is merely coincidental and plays no part in the etiology of the syndrome. It must be stated that in the absence of exophthalmos and the presence of a coincidental adenoma, the differentiation between toxic adenoma and Graves' disease is rather difficult.

Exophthalmos in Laughter.—Though the picture of chronic fright is typical of the facies of patients with exophthalmic goiter, it is not difficult to make them laugh. In fact, in these ultra-emotional patients, the alternation of frowns and moroseness with laughter occurs frequently with little or no substantial cause. Now, in a normal individual during laughter, the muscles about the eyes contract in such manner as to cause the lids to close partly over the eyeballs; in many persons this occurs to such degree that the eyes are almost closed. Such is not the case in patients with marked exophthalmos,—the eyes still stare almost as much as ever during laughter, rendering the individual's expression an odd combination of mirth attempting to temper the expression of fear.

Cause of Exophthalmos.—Experimenting on rabbits, Marañon has been able to produce emaciation, tachycardia, nervous excitability and slight exophthalmos. The exophthalmos was inconstant. In previously castrated animals, the exophthalmos appeared more constantly and more intensely. Injections of glycerin extract from a Graves' patient, herself not having exophthalmos, produced this symptom in a rabbit. The exophthalmos was observed to be accentuated by fear in the thyroid-treated rabbits. In one animal which was literally frightened to death, the exophthalmos was pronounced. This observation is in direct contradiction to the findings of other observers who claim that exophthalmos cannot be produced by thyroid administration. However, we must take into account that not all animals respond in equal degree to experimentation, and so, though results seem to differ, both schools of observers may be entirely correct. In man, there is no doubt that thyroid administration is not productive of exophthalmos unless a dis-

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tinct predisposition to exophthalmic goiter exists, in which case thyroid administration serves as the exciting cause of the syndrome.

The *modus operandi* of the exophthalmos is still a matter of controversy and interesting speculation. It is thought that this phenomenon is due to one or more of the following factors:

A deposit of fat behind the eyeball.

Continuous contraction of the levator palpebræ muscle, causing a contraction of the lids and exposure of the sclera.

Venous congestion of the posterior part of the orbit. O'Day believes that the exophthalmos is due to stasis in the ophthalmic veins, due in turn to "tetany of the ventricles."

Dilation of the retrobulbar arteries.

Hyperplasia of the orbital structures as a result of the long-continued congestion.

Contraction of Müller's muscle. This latter consists of a small group of muscular fibers located between the sphenomaxillary fissure and the supra-orbital groove.

Landstrom (quoted by C. H. Mayo) describes a microscopic muscle occurring in streaked layers in the fascia between the eyeball and tissues about it. This muscular sheath is attached forward to the lids and anterior orbital fascia. It is controlled by the sympathetic nervous system, and serves to oppose the four orbital muscles which draw the eyeball back. Irritation of Landstrom's muscle directly or through the cervical sympathetic causes exophthalmos and the concomitant drawing backward of the lids. This phenomenon is produced with the assistance of Müller's muscle.

Maurice believes that the exophthalmos is probably due to an excessive action of the adrenals.

Marine and Lenhart, however, conclude that in view of the fact that exophthalmos may occur without thyroid hyperplasia and that there may be a marked thyroid hyperplasia without exophthalmos, "both phenomena, though often not synchronous, are manifestations of a fundamental and more obscure nutritional disturbance." These authors believe that the thyroid hyperplasia is not a direct etiologic cause of exophthalmos.

It is my own opinion that proptosis is due primarily to irritation of the cervical sympathetic, following which an increase of fat occurs to fill in, so to speak, the space left by the advancing eyeball. Vascular changes, *i.e.*, dilatation of blood vessels and congestion, are also secondary to and consequent upon irritation of the cervical sympathetic and exophthalmos.

Exophthalmos From Other Causes.—Exophthalmos is most common in Graves' disease. A few other conditions may at times simulate the exophthalmos of exophthalmic goiter:

Extreme fright, in which the physiognomy assumes a picture of

terror, and the body is in an attitude of self-defense. Here the condition is bilateral and disappears on the passing away of the cause of the emotional strain.

Where the exophthalmos is so slight as to render its existence questionable, it is important and often difficult to differentiate it from the ocular protrusion of marked myopia.

Apparent exophthalmos may be due to "pop-eyes," a condition in which, because of the shallowness of the orbit, an excess of orbital fat or singularly large eyeballs, they protrude, although the patient is otherwise subjectively and objectively normal. The subject in Figures 72 and 73 is a typical example of "pop-eyes."



Figs. 72 and 73.—Case of "Pop eyes." Congenital peculiarity of the individual the subject presenting no evidences of neuro-endocrine disturbance.

Exophthalmos resulting from an irritation or pressure of the cervical sympathetic is usually unilateral, occurring on the same side as the irritated ganglion. This, among other causes, may be due to pressure from a nontoxic goiter, in which case the condition may be bilateral and with great difficulty differentiated from the exophthalmos of exophthalmic goiter. Attacks of bronchial asthma and angina pectoris, during the seizures, are often accompanied by a degree of exophthalmos, depending on the degree of dyspnea present. The same may be said of other causes of dyspnea, *e.g.*, organic heart disease and marked acute pulmonary embarrassment.

Thrombosis of the superior longitudinal sinus may give rise to a slight exophthalmos, unilateral or bilateral. There may be an apparent bulging of the eyes in paralysis of the ocular muscles.

An acute recurrent exophthalmos due to angioneurotic edema has been described.

A pathological state within or behind the orbital cavity, such as marked enlargement of the lachrymal glands, tumor or aneurysm within the orbit or of the upper jaw bone, within or outside of the antrum of Highmore, and hydrocephalus, may give rise to bulging of the eyeball. Chloromatous masses are especially liable to be the causation of ocular protraction.

Pulsating exophthalmos may be due to aneurysm of the ophthalmic artery inside or outside of the skull, pulsating orbital tumors, aneurysmal dilation of the internal carotid artery in the cavernous sinus, thrombosis of the cavernous sinus and ophthalmic vein, arteriovenous aneurysm of the orbit, pressure on the sinus by an external growth, and rupture of the internal carotid into the cavernous sinus.

I have seen a case of cyst formation in relation with the frontal bone causing pressure upon one orbit with resulting protraction forward of the corresponding eyeball.

We must also bear in mind that a slow or sudden hemorrhage within the orbital cavity, or any other substance, liquid or solid, accumulating within the orbit would tend to displace the eyeball forward.

Rondopoulo describes two cases in which exophthalmos occurred in nephritis. The frequency of occurrence of exophthalmos in nephritis was estimated to be about 3 percent., occurring mostly in subacute or chronic cases.

In a case cited by MacCallan the conclusion arrived at as a result of operation and necropsy was that the bilateral exophthalmos probably originated in an attack of cerebrospinal fever some years previously, which had cleared up and left a thickened pia-arachnoid which interfered with the return flow of lymph from the orbit. The condition, in fact, seemed to be one of lymphatic edema of the orbital tissues with most pronounced bilateral exophthalmos.

Lahey reports a case in which x-ray treatments resulted in a reduction of the pulse rate, a gain in weight and improvement of the general condition, but the exophthalmos continued to progress and ulcers of the right eye led to its enucleation. Later the left eye was removed for the same reasons, after severance of the sympathetic cervical ganglion had failed to arrest the condition.

Schietz gives details of two cases of acute lymphatic leukemia, where exophthalmos was a prominent symptom. This was demonstrated to be due to edema of the fatty tissue in the orbits.

Butler describes the case of a woman suffering from exophthalmic goiter, who had such exaggerated proptosis that the left cornea could not be covered by an effort. She rejected his advice to have the lids sutured together, and a month later was seen with an infiltrated anesthetic cornea, which soon developed an ulcer and onyx. The cornea was

incised and the lids sutured. In two days the sutures cut out, and the eye re-opened. Cauterization failed to check the spread of ulceration, and the eye was finally enucleated. The second cornea began to ulcerate, but the patient by this time was very low and soon died of heart failure.

Claiborne has seen exophthalmos and the Dalrymple sign develop within two hours in a case of violent apoplexy with convulsions, which terminated in coma. The same observer saw a case of macrophtalmos in which the eye bulged so far forward the lids barely reached the equator. In attempting to manipulate the eye, he caused the patient to jerk backward, when the lids retracted from the eyeball entirely. The patient stated that this happened to him at times, but by an effort with his fingers he could replace it.

It is not necessary to dwell in detail regarding the differential features distinguishing the exophthalmos of Graves' disease from the bulging eyeballs of other conditions. In Graves' disease the condition is usually bilateral and insidious in onset; it is usually not attended with any pain, it is preceded and always accompanied by one or more of the recognized cardinal symptoms; there are the various classical eye signs (von Graefe's, Stellwag's, Moebius', Dalrymple's, etc.), and there is the absence of other causes of exophthalmos.

Dalrymple's Sign.—This consists of retraction of the upper lid so that there is an undue separation between the two lids. The resulting widening of the palpebral fissure with the band of sclera between the lids and the edge of cornea produces the peculiar stare which is present in Graves' disease, somewhat similar to the effect produced by cocaine. In mild cases the band of sclera is seen between the upper lid and the cornea, or between the lower lid and the cornea, respectively. In marked cases, however, the band of white sclera exists above and below the cornea.

Von Graefe's Sign.—This sign is important in the early recognition of the disease. In a normal eye, when the globe is directed downward the upper lid moves in perfect accord with it. In subjects of Graves' disease, the upper lid follows tardily the downward movement of the eyeball, or, having begun its downward course, stops short of completion, the eyeball alone continuing downward. In some cases the upper lid does not move at all. This symptom is not constant, but is almost always a precursor of exophthalmos, and persists after the subsidence of protrusion of the eyeballs. If the Dalrymple sign in the primary position of the eyeball is absent, it is easily observed when the von Graefe sign is elicited, as on the tardy descent of the eyelid a rim of sclera between it and the margin of the cornea is seen. The von Graefe sign is seen best when the lid is made to descend very slowly.

Solomon Solis-Cohen describes what he terms the "*hitch*" sign of the

upper eyelid, which he considers the larval form of von Graefe's sign. When the eyelid begins its downward course over the eyeball it stops short (the "hitch"), then proceeds downward to conclude its descent imperfectly. When the lid is again raised, it does so with a continuous movement, but presents a sudden hesitancy or "hitch" in its upward course.

The Boston Sign depends upon a similar mechanism. The patient's head is firmly braced. The operator's hand, starting from the level of the patient's chin, but about 3 feet away from it, is raised upward, and the patient is instructed to follow the hand with his eyes. The operator's hand is directed downward again to the level of the patient's chin. In following the downward course of the operator's hand, the upper lid of the patient's eye will follow the pupil downward for a distance, then stop short in a "spasm" before resuming its downward course.

Stellwag's Sign.—This sign consists of imperfect power of winking or diminished frequency of the act. This may be an early sign. There may be a number of rapid winks succeeded by a long pause in which there is no movement of the lids. Each wink is incomplete; the margins of the lids do not come together as in the normal eye.

Moebius' Sign.—Moebius' sign consists in a diminution or absence of convergence. To test the convergence near point, approach a finger or pencil to the nearest point upon which the eyes can converge, which normally should be at no greater distance than $3\frac{1}{2}$ inches from the eyes or about $1\frac{1}{2}$ inches from the nose. If outward deviation of an eye occurs before this point is reached, convergence is deficient. Paresis of the ocular muscles is more characteristic than mere insufficiency of convergence (Heerfordt).

Kocher's Sign.—Kocher's sign is a slight momentary retraction of the upper eyelids on gazing at some object, if the latter is moved up and down. When following the object, the upper lid rises abruptly upward, ahead of the upward movement of the eyeball.

Tremor.—Tremor of the eyeballs is an occasional marked sign.

Rosenbach's Sign is a trembling of the upper lids when the eyes are gently closed. This is also observed in persons of a neuropathic make-up.

Suker (quoted by Zentmayer) has recently described another ocular symptom of Graves' disease. After extreme lateral rotation of the eyes to the right or to the left with the head fixed and with fixation of an object at this point maintained for a second or two, on attempting to follow this fixation point as it is rapidly swung into the median line, one or other of the eyes *fails to follow its fellow* in a complementary manner into proper convergence and for this point, when it is brought into the median line. Either the right or the left eye makes a sudden rotation into the fixation with its fellow, but before it does so, an apparent divergent strabismus is manifested. Suker believes this phenomenon due to a dissociation in the functions of the sympathetic and the extra-

ocular motor nerves of the eye, and perhaps also to exhaustion on extreme lateral rotation of the eyes.

The Jellinek-Teillaïs Sign.—This sign is a brownish discoloration of the eyelids and is seen as a ring around the orbit. The discoloration is of a deep brown, occasionally almost violet hue and occurs in 10 to 25 percent. of all cases of Graves' disease. Sainton and Fayolle state that it is often a feature of the earliest stage of the disease, later almost disappearing, with subsequent recurrence. Brown spots elsewhere on the body may coexist, suggesting the stain of iodin on the skin.

A not uncommon phenomenon is a *falling out of the eyebrows* and eyelashes, which is an accompaniment of the alopecia frequently met with in Graves' disease.

Nystagmus is rarely observed.

Clifford's Sign is the difficulty of evertting the upper lids. This phenomenon is an almost constant sign.

A feeling of *pressure* behind the eyes is frequently complained of by patients presenting marked exophthalmos.

Preble notes an abnormal *dryness* of the eyes in a certain percentage of cases.

On the other hand, *epiphora* or abnormal *lachrymation* is seen in many instances.

Reisman describes a *bruit* over the eyeball, synchronous with the heart beat. The bowl of the stethoscope is placed over the closed eyelid. The phenomenon is inconstant. The same sign is obtainable in aortic regurgitation. Reisman does not claim priority in the detailing of this sign, stating that it has been reported by Snellen, Donders, Hunter, Carrington, and Drummon. Herring claims that murmurs over the eyeball are of muscular origin, heard when the eyelids are closed and disappearing when muscular contraction ceases.

Curschmann and Loewi have observed in a considerable percentage of cases of Graves' disease, that installation of *adrenalin* results in *mydriasis*. Curschmann (quoted by McCarrison) notes that in many instances the eyes present the phenomenon just the *reverse of the Argyll Robertson pupil*, i.e., there is reaction to light, but not to convergence.

Ulceration of Cornea.—Ulceration of the cornea, as intimated, is not an uncommon occurrence. The function of the eyelids as protectors of the delicate ocular conjunctiva being diminished, the lids being unable to close over the protruding organ, the eyeball is exposed to the air day and night; indeed, even winking is for that reason less frequent and less complete. As a result of this exposure, chronic conjunctivitis and corneal ulceration may occur, leading occasionally to partial or complete blindness, and if infection becomes marked, to panophthalmitis, so that an urgent necessity for enucleation may arise. Rogers reports a case of corneal ulcer in exophthalmic goiter in which, because of the extreme degree of exophthalmos and edema of the conjunctiva,

various procedures were attempted to relieve the pressure and to protect the cornea from further erosion. Ligation of the inferior thyroid arteries and section of the lower filaments of the cervical sympathetic, and treatment with adrenal extract gave no relief. The lateral bony walls of the orbit were then partially removed, and the eyelids were sutured together after longitudinal incisions were made in each. This last procedure alone gave relief and protection to the cornea.

Ocular Tension.—Imre finds that there is a disturbed regulation of ocular tension in Graves' disease. He states that more have high tension than low tension; several with decidedly low tension were seen, however. In his experience Graves' disease can cause either type of abnormal eye tension. But in either case we find almost regularly a remarkable difference of tension between the right and the left eyes, and a pronounced lability of the tension even during measurement.

Ophthalmoscopic Changes.—These are not marked or typical. There may be a dilatation of the arterial vessels, their caliber becoming equal to that of the veins. Arterial pulsation is frequently discernible.

Optic Atrophy.—This may occur as a late sequel. According to Sattler the occurrence of retrobulbar neuritis in Graves' disease is very rare and has not hitherto been described as an initial symptom. He records a case of Graves' disease in which a diminution of visual acuity was the first thing that induced the patient to seek medical advice. All other possible causes of the neuritis could be excluded. A few other cases have been reported in which, on improvement of Graves' disease, the optic neuritis subsided. There are also cases on record of misuse of thyroid tablets being followed by retrobulbar neuritis, and finally Sattler found that experimental administration of thyroid tablets to animals produced a disease of the optic nerve resembling toxic amblyopia.

An editorial in the *New York Medical Journal* calls attention to the effects upon the optic nerve by the stretching from the proptosis. The first effect of this traction is borne by the fibrous sheath of the nerve, and as it is resistant, the elongation occurs slowly. Hence the nerve does not as yet suffer, while the ciliary nerves, which lack protection of this kind, are more or less tense. But finally the sheath becomes so elongated that the nerve will be directly submitted to the effects of traction. Hence the development of special disturbances whose evolution will follow the oscillations of the exophthalmos. The degree of elongation to which a nerve can be subjected without serious symptoms varies widely. Marked exophthalmos may not cause any disturbance of the optic nerve, while less pronounced cases rapidly cause a loss of visual acuity. In certain cases lesions persist as purely functional disturbances for a long time and visual acuity becomes normal as the exophthalmos diminishes. In the first place the disturbances are purely functional; such symptoms as hyperesthesia of the retina, photophobia,

and others may be observed. This phase is succeeded by a phase of depression in which all the symptoms of paresis met with at the onset of progressive optic nerve atrophy may be noted. But the amblyopia rather constantly presents certain peculiarities of importance, in that they allow one to distinguish it from that due to optic nerve atrophy. If the exophthalmos is accentuated the phenomena of the second phase develop. One of two conditions will be met with. Either the tension of the nerve will result in a true neuritis whose traces will remain for a long time, or else the trophic system of the optic nerve will be involved and a veritable atrophy ensue, which will be readily detected by the ophthalmoscope. But in exophthalmic goiter these lesions of the optic nerve hardly ever attain an extreme degree. That blindness does not occur is probably due to the fact that the exophthalmos, even in the most pronounced cases, never extends beyond a certain limit and that generally it does not remain long enough in a pronounced degree for structural lesions of the optic nerve to become generalized.

Vision, though not materially affected, may be altered in advanced cases. In addition to corneal ulcers and conjunctivitis interfering with vision, the weakness of the ocular muscles as part of the general muscular weakness adds to the difficulty. All these, with the occasional deficiency of convergence and sluggishness of pupillary activity, result in impairment of accommodation. Sourasky reports the refraction errors in 20 patients, 16 of whom had exophthalmos of varying degrees. In the 32 eyes with exophthalmos the disturbances were distributed as follows: hypermetropia, 1; simple hypermetropic astigmatism, 1, compound, 13; myopia, 2; simple myopic astigmatism, 7, compound, 5; mixed astigmatism, 3; i.e., 29 out of 32 eyes had astigmatism, 14 had hypermetropic astigmatism and 12 myopic astigmatism. This is a higher incidence of astigmatism than is usually found and the proportion of myopic to hypermetropic astigmatism is increased. In the 4 cases without exophthalmos the distribution was: compound hypermetropic astigmatism, 6; compound myopic astigmatism, 1; myopia, 1. Headache was present in a large percentage of the cases. This was relieved by the use of properly fitted glasses.

Rôle of Ophthalmologist in Graves' Disease.—It can readily be seen that the coöperation of the ophthalmologist in the management of a subject of Graves' disease is not only desirable, but often vital. The maintenance of a healthy conjunctiva, the prevention of corneal ulcers and opacities, the correction of refractive errors with its conservation of nervous energy, the occasional examination of the fundus to detect any changes suggesting circulatory and renal complications or an intercurrent diabetes,—this is the important rôle of the oculist whose services should always be considered as a necessary constituent in the rational outline of the treatment of these patients.

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CHAPTER XIV

MISCELLANEOUS SYMPTOMS OF EXOPHTHALMIC GOITER

THE GASTRO-INTESTINAL TRACT

GASTRO-INTESTINAL symptoms in exophthalmic goiter are the rule, with few exceptions. Beginning with a mere sensation of discomfort after eating, these manifestations may become so serious, with incessant nausea, vomiting, and diarrhea, as to dominate the syndrome and endanger the life of the patient. If the patient is to gain weight and strength through an intake of the great amount of food vital to recovery, it is only through a good digestive tract that the goal is reached and the patient saved to health and usefulness.

The **Teeth** and **Gums** are frequently in poor condition, and pyorrhea alveolaris may be present and bear a causal relationship to the disease, though more often this is merely coincidental. However that may be, dental attention must be insisted upon, both from the viewpoint of elimination of focal infection and perfection in the mastication of food.

The **Tongue** may or may not be coated, depending upon the severity of existing digestive disturbances. In the presence of good digestion, the tongue presents no characteristics except a coarse tremor on protrusion in the majority of typical cases.

The **Saliva** is at times diminished, but an increased output is more commonly seen. Occasionally the sialorrhea is quite as troublesome as in the extreme cases seen by obstetricians in pregnancy.

Dysphagia, so commonly seen in toxic adenoma, is rarely encountered as a pressure symptom in exophthalmic goiter. A feeling of a "ball in the throat," however, is commonly complained of, even by patients with no evident thyroid enlargement, and is to be attributed to *globus hystericus*.

The **Appetite** in exophthalmic goiter varies widely. Anorexia, dependent upon poor digestion, is less often met with than a normal or even a very good appetite. The occasional ravenous appetite and thirst, coupled with the persistent loss of weight and strength and carbohydrate intolerance, so closely resemble diabetes mellitus in the clinical picture that the diagnostician must be on his guard. Especially is this true in the absence of exophthalmos and of goiter. In general, the appetite is good, but easily satisfied and capricious. Thus, the meal is begun ravenously, but after the first few morsels the patient stops eating, only

to feel hungry again an hour or two later when another few mouthfuls are eaten. The patient, though seeming to eat all day, in reality does not assimilate a quantity of food consistent with normal conditions. If we take into account the fact that these patients, by reason of their loss in weight and continued overactivity of catabolic processes, must consume at least twice as much food daily as under normal conditions, it can readily be seen how important it is to train the digestive tract to serve as our ally in the process of forced feeding.

Nausea and **Vomiting** with other miscellaneous evidences of *nervous indigestion* are commonly observed. These patients frequently suffer with gastric hyperacidity and pyloric spasm. The vomiting and gastric distress may become so severe as to endanger the life of the patient. This is especially true when the vagotonic symptoms predominate. In a few of my patients there was a previous history of treatment for a primary gastric disease for months or years before the correct diagnosis of Graves' disease was finally decided upon. Thus valuable time was lost, during which marked damage to the vital organs occurred. Gastric ulcer is a not uncommon diagnosis when the gastric symptoms are particularly violent. These gastric manifestations, with gradual loss of weight and strength, may precede for a variable time the frank manifestations of Graves' disease and mask them for many months. In older patients, evidences of gastric atonia with hypochlorhydria may occur.

The condition of the gastro-intestinal secretions during an attack of Graves' disease is still a question of considerable interest. Herzfeld, for instance, finds that in the majority of patients there is a hypoacidity or an acidity of the gastric juice. While this may be true of a small percentage of instances, especially in persons past the age of 40, I find the average patient presenting evidences of hyperacidity. Gyotoku in an examination of the duodenal fluid in 20 cases of Graves' disease finds the enzymes below normal in 60 percent. He found no relationship existing between achylia and the quantity of gastric juice secreted, nor did he discover any relationship between the quantity of the duodenal fluid and disturbances of carbohydrate metabolism.

In a recent patient of mine, the gastro-intestinal crisis had focussed itself about the upper right abdominal quadrant, and the patient was erroneously operated upon on a diagnosis of *cholelithiasis*. The gall bladder was found to be normal, and it was only during the post-operative convalescence that a diagnosis of Graves' disease was made. Again, the right lower quadrant of the abdomen may be the seat of marked subjective symptoms, simulating an attack of acute *appendicitis*. Here, too, operation is occasionally performed only to lead to a subsequent diagnosis of Graves' disease.

Constipation occurs in the minority of patients, existing either as an etiological factor or as a coincident. Of course, constipation is

preferable to diarrhea, as its control is a far simpler problem. Care must be taken, however, not to employ drastic purgatives, lest constipation be converted into a dangerous diarrhea.

Diarrhea is common and may be either constant or alternate with periods of constipation. Diarrhea and indeed vomiting are evidences of a severe and often protracted syndrome of Graves' disease. Both are often intractable and stubborn to treatment, wearing out the patient's lagging vitality and trying the soul of the medical attendant. In rare instances, diarrhea may become so severe as to terminate in intestinal hemorrhage. It is interesting to note that if, during the satisfactory progress of the patient as the result of treatment, there occurs a sudden emotional shock or psychic trauma, nausea, vomiting, and diarrhea are apt to herald an exacerbation or relapse, even though the patient never complained of these symptoms before. The character of the feces varies widely. They may be normal or present traces or quantities of blood. Often one may observe the features of pancreatic and biliary disease, with clay-colored stools containing fat and undigested meat fibers.

THE CUTANEOUS SYMPTOMS

The skin in Graves' disease presents phenomena of clinical and diagnostic interest. It is thin and moist to the touch, and if a finger is kept in contact with any part of the body surface for a few seconds, with moderate pressure, its removal will be followed by an area of pallor corresponding to the finger mark, which in a few seconds fades away, giving rise to a pinkish hue which remains for from a fraction of a minute to a minute or more.

The skin in exophthalmic goiter is in the majority of patients of a plethoric hue and somewhat greasy from the excessive secretion. There may be a degree of secondary anemia or chloro-anemia which is not evident on the surface because of the partial vasomotor instability of the peripheral arterioles. Of course, areas of edema,—the ankles, legs or elsewhere, due to cardiac failure, will appear pale and doughy, and pit on pressure. This must not be confused with the pale, doughy skin of myxedema, which does *not* pit on pressure. Occasionally in a Graves' subject there is observed such an area of swelling of the ankles, which indicates an admixture of a degree of hypothyroidism within the syndrome of Graves' disease. The temperature of the skin in subjects of exophthalmic goiter is frequently a degree or two above normal.

Pigmentation is commonly seen, and as elsewhere mentioned, suggests the implication of the adrenal glands in the Graves' syndrome. The percentage of cases in which pigmentation is found varies with the observation of different authors; some claim to have observed pigmentation in as high as 70 percent., others in but 10 percent. of their respective series. According to Falta increased pigmentation is seen in

50 percent. of patients with exophthalmic goiter; Kocher places the figure at 30 percent. Sainton and Fayolle have seen it in 25 percent. of their series of cases and describe four principal varieties of this pigmentation: (1) localized pigmentation; (2) more or less diffuse pigmentation;

(3) Addisonian melanoderma with pigmentation of the mucous membranes; and (4) generalized pigmentation of Addisonian type with discoloration of the mucous membranes. The localized form of pigmentation shows a predilection for the face. It consists sometimes of small brown spots somewhat larger than common nevi; in other instances there may occur brown patches extending into the region of the neck. In my series of cases approximately 20 percent. presented Addisonian manifestations in varying degree.



FIG. 74.—Exophthalmic goiter with marked pigmentation.

Hyperidrosis, or excessive sweating, is common and very annoying to the patient, and gives rise to the increased electric conductivity of the skin (Vigouroux). Sweating, occurring especially at night, in an emaciated, weakened

patient with a slight rise in temperature, dyspnea, and diminished respiratory expansion, may lead to a tentative diagnosis of pulmonary tuberculosis. In addition, this symptom must not be confused with the sweating seen in the following conditions: the crisis of fevers, marked physical and mental strain, great weakness and collapse, the debility of convalescence, infections and septic conditions, and the action of diaphoretics. Sweating of the palms of the hands and soles of the feet is especially characteristic of Graves' disease. The cold, clammy hand of the subject of Graves' disease is peculiarly noticeable during a hand shake, the perspiration of the patient being imparted to the hand of the other person. Hyperidrosis may be so troublesome as to become one of the causes of insomnia. In many patients this symptom is bitterly complained of, and it may be necessary to change the bed linens two or three times every night for months.

Dermographia is constantly present in exophthalmic goiter and is regarded by Solis-Cohen and others as an evidence of vasomotor ataxia. With a blunt-pointed probe, or the edge of a silver coin, or even the dorsal aspect of the finger nail, markings or letters are traced out on the patient's skin,—usually the back, employing moderate pressure. Following the immediate pallor of the tracings, there will be a reddening within 8 to 10 seconds, which, reaching the maximum

hue within a half minute, begins to fade 20 to 30 seconds later. I have observed that the promptness of occurrence and degree of intensity of the dermatographic markings vary with the severity and duration of Graves' syndrome. In the early mild forms of the disease dermatographia is not very marked and disappears within one minute, while in the very severe patient the tracings are very distinct, often raised, and may not disappear for from 5 to 10 minutes. In a small percentage of cases of mild or moderate severity, instead of a red tracing, the dermatographia will be pale or white; this is believed by some observers to be an evidence of marked adrenal involvement. Again, dermatographia may be white during the first 10 or 20 seconds, gradually changing to red, which latter fades away in the course of a minute or two. Often we find the usual red dermatographia bordered by a margin of pallor which gradually merges off into the color of the skin beyond.

Erythema.—I have observed that in all instances of thyroid hyperactivity, whether they be true exophthalmic goiter or toxic adenoma, the skin of the upper anterior aspect of the chest, from the neck downward, is erythematous, the lower border of the area appearing as a rounded margin with the convexity downward, not unlike the shape of a baby's bib, blending sometimes rather abruptly, at times gradually, into the normally appearing skin below. Pressure upon, then removal of the examining finger from this area leaves a pale mark which disappears within a few seconds. Erythematous areas or blotches are commonly seen elsewhere and are evanescent in occurrence. Indeed, the areas of pressure of clothing are more or less constantly erythematous in many patients. Kahane describes a form of vasomotor irritability which he terms "galvanopalpation." The negative electrode is attached to some distant portion of the body. The positive electrode, which should be sharp, is then lightly applied on the skin over the thyroid gland. If the pain reaction is intense and there is a marked redness which persists for a long time, the thyroid gland is considered to be functioning to excess. It is necessary for comparative purposes always to use a galvanic battery of standard strength.

Lian, in making examinations of soldiers complaining of palpitation, found in a number of instances a hypersensitivity of the skin over the thyroid gland. This area may follow closely the margins of the organ, or may cover one or both of the lobes or the isthmus. In many instances the thyroid is already swollen. Lian regards this sign as diagnostic of the early stages of exophthalmic goiter. Marañon regards as a test for hyperthyroidism a redness in the region of the thyroid following the rubbing of the skin lightly with the fingers. This is really dermatographia which may be demonstrated anywhere on the patient's skin.

Pruritus of varying degree, often as troublesome as that occurring in diabetes mellitus, is occasionally encountered.

Urticaria is occasionally observed, especially where the gastrointestinal symptoms are severe.

Eczema is frequently seen during the active stages of the disease.

Psoriasis, widespread or local, may precede the syndrome of the disease for years and may be markedly improved or even disappear on recovery.

Scleroderma, usually more or less circumscribed, has been observed in many instances. The reports of scleroderma in exophthalmic goiter are becoming more numerous in recent years.

Petechiae most often occurring over the front and upper portion of the chest, are of some diagnostic importance.

Angioneurotic Edema is occasionally observed in patients suffering with exophthalmic goiter and suggests a common vasomotor and neurotic etiology.

Trophic Edema associated with Graves' disease is rare. In 1920, Parhon and Stocker reported the case in a woman of 21 in whom trophic edema beginning at the instep of one foot, progressed upward, soon involving, first the one entire limb, then the other. In the perusal of the literature these authors discovered but 25 cases of the association of trophic edema with Graves' disease.

Peripheral Stimuli are most rapidly conducted, more acutely and intensely translated, and the responses are exaggerated.

Indicating loss of occipito-frontalis control, *the forehead is smoother than in health, with failure to wrinkle on looking up* (Joffroy).

The Hair, including the eyebrows and lashes, may become brittle and fall out. Alopecia is common, though not of special importance.

The Nails may become brittle and weak.

RESPIRATORY SYMPTOMS

Chronic Rhinitis, Sinusitis, and especially chronic *tonsillitis* and *pharyngitis* which may play an important etiological rôle, may be found in these patients on physical examination.

The **Voice** in patients with Graves' disease is commonly stridulous, weak, high-pitched, and often tremulous, in some respects resembling a voice during paresis of the vocal cords. Hoarseness and cough are not uncommonly observed in exophthalmic goiter. These symptoms are usually due to a compression and irritation of the inferior laryngeal nerve by the enlarged thyroid, irritation and compression of the muscles about the larynx and of the vocal cords, or they may be produced by a preexisting primary morbid condition of the throat or larynx. If cough is due to a coexisting phthisis, it may be associated with expectoration of variable character. An enlarged thymus is rarely responsible for cough and paroxysmal attacks of choking. Rarely, in cases of accentuated nervous phenomena, these symptoms may be of hysterical origin.

Diminished Respiratory Expansion and an increased respiratory rate are common in Graves' disease. This is due to the quickening of metabolism, muscular weakness, excitation of the respiratory center by the circulating toxins, and in some instances the presence of latent or active phthisis. A flattening of the anteroposterior diameter of the chest is frequently observed.

Pulmonary Tuberculosis associated with Graves' disease has been the subject of considerable attention; remarks concerning this relationship have already been made in the chapter on pathogenesis. Caro found signs of an apical process, probably of tuberculous origin, in 210 out of 486 men with thyroid symptoms, and Schinzinger found a tendency to goiter in 355 out of 521 tuberculous patients. Only 191 of these 355 patients had symptoms suggesting exophthalmic goiter. Swan, in his series of 50 cases, states that 2 had definite evidence of pulmonary tuberculosis, 6 had suspicious apices, and 4 had chronic pleurisy.

In my own series of exophthalmic goiter cases, I find distinct evidences of incipient, latent, or mildly active phthisis in approximately 4 percent. The pulmonary status almost invariably ceases to exist as a menace and the symptoms disappear during the course of dietetic, hygienic and medicinal treatment applied toward recovery from the Graves' syndrome. Gallotti also describes 6 cases of insidious tuberculosis associated with symptoms of exophthalmic goiter and believes that treatment of the Graves' condition exerts a favorable influence on the pulmonary condition. He has encountered so many cases of this combination that he now suspects pulmonary tuberculosis in every case of exophthalmic goiter until this can be excluded. His experience indicates further that enlargement of the thyroid seems to imprint a benign character on the tuberculosis.

Hofbauer believes *asthma* to be a manifestation of Graves' disease. Curschmann (quoted by O. H. Brown) reports two cases of Graves' disease associated with asthma. He believes that asthma and Graves' disease may both result from sympatheticotonia or vagotonia.

HYPER- WITH HYPOTHYROIDISM

Symptoms of *hyperthyroidism with hypothyroidism* may appear simultaneously in a patient suffering with Graves' disease. This apparent paradox in the clinical picture is a strong argument in favor of the dysthyroidism, pluriglandular, detoxication, and neuro-endocrine theories, and a convincing argument against the hyperthyroidism theory offered in explanation of the pathogenesis of Graves' disease. Symptoms of hypothyroidism may precede those of hyperthyroidism in Graves' disease, and there are writers who are firm in their belief that this is invariably the case. I have not been convinced of the

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truth of this hypothesis, but have, in common with many others, observed evidences of thyroid hyposecretion associated with, and at times alternating with manifestations of hypersecretion as constituents of the clinical picture of Graves' disease. I have occasionally observed distinct myxedematous signs and symptoms following a typical course of the affection. It is in these patients that the occasional good report from thyroid ophotherapy is obtained.

The admixture of distinct hypothyroidism within the symptomatology presented by these patients is not infrequently due to surgical intervention with the swollen thyroid gland. In this affection the patient actually needs all the thyroid hormone the gland can manufacture for a successful defense against causal toxins arising elsewhere in the body. Hence the organ undergoes hyperplasia during the course of the disease. Interference with this defensive reaction by a curtailment of secretion through surgery or x-rays is synonymous with a prolongation of the course and often an increase in the severity of the syndrome. Thus we find that patients presenting scars of one or more thyroidectomies suffer with a rather aggravated Graves' syndrome simultaneously with all the evidences of a variable degree of hypothyroidism. This is an artificial production of hypothyroid symptoms. There is also a natural mechanism over which we have but little control. The thyroid during the active stages of Graves' disease is so overworked because of demands made upon it for its protective hormone, that in course of time the organ begins to undergo degeneration and slows down. Some of the symptoms seem to become ameliorated; the weight is increased, and the patient seems to be approaching spontaneous cure. But the thyroid continues to degenerate, and soon the secretion is barely sufficient to maintain metabolic equilibrium. Thus, shortly after relatives and friends rejoice at the apparent recovery of the patient, it is seen that he continues to gain in weight considerably beyond the normal figure, the features gradually become stupid and expressionless, the skin becomes dry, pale, and doughy, speech is slow and monotonous, cerebration is tardy and somnolence is continuous. We have here a case of hypothyroidism or myxedema due to the so-called "burned out" thyroid. It is not difficult to conceive of a sort of transitional stage in the above-mentioned process during which symptoms of both hyper- and hypothyroidism co-exist for a variable period of time, or even a lapse of time during which hours or days of apparent manifestations of hyperthyroidism alternate with like periods of hypothyroidism or *vice versa*.

THE GENITO-URINARY TRACT IN EXOPHTHALMIC GOITER

The symptoms of Graves' disease referable to the genito-urinary tract, though numerous and important, are inconstant. A few clinical manifestations are, however, characteristic. We shall subdivide the

subject into symptoms referable to the genital functions, and those referable to the urinary functions.

SYMPTOMS REFERABLE TO THE GENITAL FUNCTIONS

The functions of the thyroid and other endocrine organs are intimately related to those of procreation, and abnormalities of the former are apt to lead to malfunction of the latter. The vegetative nervous system also plays its part in the production both of the syndrome of Graves' disease and of dysfunction of the genital organism, and in the presence of the Graves' syndrome, it serves as a kind of *liaison* in the production of the various subjective and objective genital symptoms.

Menstruation may undergo marked variations from the normal. *Amenorrhea* is frequently observed to persist for many months. This may occur particularly in instances of marked emaciation and asthenia, the menstrual cessation being an effort on the part of Nature to conserve the bodily forces. The menstruation may be irregular in occurrence, duration, and quantity,—now on time, now too soon, again delayed, at one time diminished, at another time very profuse and weakening. Since in exophthalmic goiter there is diminished coagulability and viscosity of the blood, at times approaching hemophilia in character, menstruation may in isolated cases become so profuse and protracted as to occasion much concern and necessitate corrective therapeutic measures.

Engagement.—The state of "engagement" is commonly replete with moments of emotionalism which are capable of aggravating the syndrome of Graves' disease. Indeed, in not a few instances, I have observed that this situation has played a direct etiological rôle in the production of the disease.

Libido, Potentia, and Fecundity.—In both sexes, in the presence of Graves' disease *sterility* is common, but not the rule. In the male who had not been sterile prior to the onset of the syndrome, I have observed an *increased fecundity*. Indeed, the sexual activity of the patient is at times increased to such a degree that it constitutes an important problem in treatment. *Priapism* may require special therapeutic attention. The patient's moral sense may become all but eliminated, and gratification may be sought away from his own household. *Sexual excitability* increases the endocrine dysfunction, especially that of the thyroid; the latter seems in turn to increase the sexual excitability. Thus there is added another vicious circle to those already characterizing the affection.

In the female suffering with Graves' disease, though the libido may be normal or acute, there frequently occurs a degree of *vaginismus* and a dread of coitus. Often this status bears an etiologic relationship to Graves' disease. Here, also, the vicious circle obtains: ungratified

desire leads to an aggravation of the syndrome of Graves' disease; the aggravated syndrome in turn leads to increased libido. In consequence of diminished frequency of coitus and because of the probable co-existing menstrual disturbances and ovarian hypofunction in these patients, there may be sterility in some instances and lessened fecundity in others, especially during the active stages of the disease. Many patients become pregnant, however, and when this occurs, other problems may arise.

Pregnancy.—The clinical implications arising from a combination of exophthalmic goiter or Graves' disease and pregnancy in the same individual are noteworthy. The problem is important and often difficult, for upon its solution depends the life both of the patient and the offspring. During the past decade I have seen a considerable number of subjects of Graves' disease in whom pregnancy was a factor, and I believe that the topic deserves the serious attention both of internist and obstetrician. Pregnancy, in a goodly percentage of cases, seems to have been the exciting cause of Graves' disease. But in the majority of patients in whom exophthalmic goiter had been present at the time of conception, pregnancy serves somewhat to ameliorate rather than aggravate the syndrome. Especially is this true if the disease has not led to marked degeneration of the vital organs, and if the patient is under the care of a well-equipped internist who understands the management of these subjects. However, in many patients a moderate aggravation of the syndrome, especially the thyroid swelling, may occur in pregnancy, to disappear shortly after delivery. On the other hand, the occurrence of pregnancy in a markedly advanced case of the disease is usually detrimental, as the vital organs are unable to cope with the increased demands made upon them. Sooner or later Nature either expels the uterine contents, or, if this does not occur, the physical condition may require a therapeutic abortion. Premature expulsion of the uterine contents occurs, not in the majority of patients as is taught in some quarters, but in the minority of instances, depending upon the severity of the Graves' syndrome during pregnancy. In patients whose progress is satisfactory, the woman who is delivered of a live baby at full term is better off than she who had miscarried; the reasons are (1) *mental*, because of the happiness and contentment of motherhood, and (2) *physical*, the tendency toward spontaneous rectification or adjustment of interglandular relationship following normal delivery at term. A patient who has recently miscarried and whose maternal instinct is very strong is apt to become a comparatively difficult case to manage.

Parturition (Advice to Obstetricians.)—Parturition in a subject of Graves' disease is fraught with at least two problems. The first is that of straining with each pain. Bearing down not only adds to the undue strain of an overworked heart, but also increases the size and



FIG. 75.—Exophthalmic goiter during early pregnancy.



FIG. 76.—Same patient as in Fig. 75, during eighth month of pregnancy, presenting aggravation of the syndrome with marked emaciation.



FIG. 77.—Same patient 5 months after delivery; disappearance of exophthalmos and goiter; the patient progressing toward recovery.

vascularity of the thyroid gland. In addition, the accompanying pain is a kind of shock which had preferably be avoided. I advise the obstetrician to employ his art in such manner as would obviate the necessity for bearing down, by the use of a few whiffs of chloroform or other measures which may be deemed advisable at the time. The second problem is that of post-partum hemorrhage. The coagulation time of the blood in a subject of Graves' disease is delayed, in some instances to such an extent that the patient should be managed with the same degree of caution as a subject of hemophilia. I suggest the use of prophylactic injections of a reliable horse serum product or similar preparations during labor. It is essential also to be in readiness for packing the uterus after delivery of the placenta. Post-partum injections of pituitrin and ergot in large doses by mouth are harmless and frequently useful in this connection. Finally, it is well for the obstetrician not to leave the patient for at least two hours after delivery is completed.

Lactation.—Lactating mothers suffering with Graves' disease do not progress favorably until lactation is discontinued. The patient is already suffering with a high plus basal metabolism, and a further drain of the body makes for a greater loss in weight and an aggravation of the disease. Lactation must be discouraged after the first week or two, and the baby should be fed by a wet nurse or placed on an artificial mixture as soon as possible. I have often seen a very miserable patient improve with surprising rapidity very soon after breast feeding was discontinued. Moreover, the infant in taking the milk of such a mother is receiving food contaminated with the toxins of Graves' disease. It is evident, then, that such infants do far better away from the mother's breast.

Effect of the Mother's Graves' Disease on the Infant.—Theoretically, a child born of a mother with Graves' disease would be either predisposed to or afflicted with an endocrinopathy. However, my observation of a goodly number of these youngsters, some of whom are attending school, proves them to be enjoying the average good health, and a few appear to be exceptionally robust. What puberty and adolescence have in store for them remains to be seen; attempts at prophylaxis in these persons should be seriously considered. There is one peculiar phenomenon which is noteworthy in this relation. Occasionally, *an infant born of a mother suffering with this affection may present congenital goiter with or without evidences of hypothyroidism or of cretinism.* Several observers have called attention to this occurrence, and I have seen three instances of this sort in the past few years. This should give the surgeon much food for thought, as it presents one of the most striking arguments against thyroidectomy in this affection.

Repeated Pregnancies.—Sufferers from Graves' disease are not as apt to become multiparae as normal women, for reasons already implied.

If, during the active course of the disease pregnancies succeed each other frequently, and the patient's resistance is great enough to be delivered of living children at full term, there follows a tendency toward spontaneous recovery of the Graves' syndrome and thyroid hyposecretion. This is preceded by a period of time during which a combination of hypo- and hyperthyroidism characterized the symptomatology, especially during and shortly after pregnancy.

Associated Pelvic Lesions.—The gynecologic lesions often found to coexist with the Graves' syndrome have given rise to the assumption that they are causally related to the endocrine, especially the thyroid dysfunction. This is apparently proved by the many instances brought to our attention in which a pelvic operation with the removal of the offending lesions has cured the exophthalmic goiter. Moreover, the correction of certain abnormalities of the uterus or adnexa by x-ray exposures has also resulted in the amelioration of the symptoms of exophthalmic goiter in isolated instances. In these cases, the syndrome is associated with pain, menstrual disturbances and reflex phenomena characteristic of the existing pelvic lesion.

SYMPTOMS REFERABLE TO THE URINARY SYSTEM

Increased Frequency of Urination, diurnal and nocturnal, are the main symptoms presented by the urinary system. Aside from the discomfort of bladder irritability during the day, many patients are obliged to arise several times every night. Thus we have another cause of insomnia. *Polyuria* and increased frequency of micturition often seen in Graves' disease are troublesome symptoms. Some of my patients were compelled to rise as often as ten or twelve times every night to relieve the bladder. The cause of this symptom is not clear, but it is probably due to several factors, among which may be mentioned the increased tissue oxidation, the polydipsia, the hyperglycemia, the irritability of the kidneys, and the neurosis of the bladder. Polyuria may for weeks or months be a forerunner of exophthalmic goiter.

Glycosuria in varying degree is commonly seen in exophthalmic goiter and may be experimentally produced in normal persons by thyroid administration. This is due to the carbohydrate intolerance resulting from the depressing effect exerted by the toxemia on the pancreatic functions. The greater the severity of the syndrome the greater the carbohydrate intolerance until, in advanced cases, we are confronted with a symptom-complex which may in some instances approximate in character a full-fledged case of diabetes mellitus as a complicating or intercurrent affection.

Albuminuria (usually transient) is occasionally present and is due to a coexisting nephritis, an irritation of the kidneys by the oversupply of the causal toxins in the blood, the passive congestion consequent

upon cardiac incompetency, or to a combination of these causes. It rarely assumes alarming proportions and is occasionally accompanied by hyaline and granular casts.

The accelerated total metabolism in Graves' disease gives rise to an increase in the output of the urea nitrogen, total nitrogen, uric acid, and the phosphates in the urine. That the creatinin content of the urine is greatly reduced was pointed out by Forschbach in 1907; the addition to the diet of meat extracts and other purin-producing substances was unable to effect an increase of creatinin in the urine.

ARTIFICIAL OR FACTITIOUS GRAVES' DISEASE

Artificial or "factitious" Graves' disease must be differentiated from the usual form of the disease. The ingestion of iodin or thyroid extract may be responsible for the symptomatology, depending upon whether the individual affected has been susceptible to Graves' disease prior to the taking of these drugs. Taken in sufficient dosage, iodin and thyroid extract are quite as likely to act as exciting causes of Graves' disease as psychic traumata. Thus, instead of an emotional or psychic torch, there is a chemical one which flares up into the conflagration of Graves' disease, the inflammable material represented by a neuro-endocrinopathic subject.

But the usual result of indiscriminate iodin and thyroid administration is a pseudo-Graves' syndrome or "artificial Basedow." "Iodin Basedow" is the term applied to the symptomatology presented by a patient as a result of taking iodin or the iodids. Rarely, this condition may be produced by the local administration of tincture of iodin in persons possessing an idiosyncrasy to the drug. At first there are observed in varying degree the classical symptoms of iodism, *viz.*: coryza, evidences of gastro-intestinal and bronchial catarrh, lachrymation, conjunctivitis, salivation and the typical skin eruptions. Sooner or later there is a development of palpitation, tachycardia, nervous irritability, tenderness over the thyroid gland, and other evidences of *hyperthyroidism*. The most usual cause of "Iodin Basedow" is the indiscriminate use of iodin or the iodids in the treatment of simple goiter. Either through patent medicines containing iodin, its administration by a physician, or through the advice of a friend, the patient, anxious to rid herself of a goiter, takes iodin in improper doses or for an undue length of time. Even in instances where a physician has administered the drug with proper scientific consideration, the patient is apt to continue the drug without being observed by the doctor until she must again return to him for relief of alarming constitutional symptoms. Often the goiter, for the relief of which the drug was taken, becomes distinctly larger in size and may become tender. In any event, the ultimate result is hyperthyroidism, practically identical with

the condition seen in toxic adenoma. The only difference between these two forms of hyperthyroidism is that the factitious form is apt in a percentage of cases to disappear on the discontinuance of the drug.

The unscientific use of thyroid extract gives rise to practically the same state of affairs without the preliminary symptoms of iodism. The drug, administered primarily for the relief of simple goiter or of obesity or hypothyroidism, is taken by the patient, often through the wiles of patent medicine firms, without scientific guidance. Often enormous doses are consumed in a comparatively brief period. Sooner or later, the patient feels a sensation of constant trembling, there is palpitation, loss of weight, weakness, incapacity for the usual daily duties, and all the other evidences of hyperthyroidism. The administration of thyroid extract is in all cases fraught with great danger unless taken in small doses at first, and the patient is carefully observed at short intervals by the attending physician. Most instances of artificial thyroid intoxication are due to the ignorance of the patient, which fact is occasionally a reflection upon the physician because of his neglect to warn his charge of the potency of the drug and the possibility of harm from its unguided use.

VAGOTONIA AND SYMPATHETICOTONIA

The autonomic or vegetative nervous system, that division of the nervous system which is concerned with the vegetative or vital processes of the body and over which the will has no control, is intimately related to the endocrine organs and inseparably associated with the pathogenesis and symptomatology of exophthalmic goiter. Voluminous and very interesting literature on this subject has been contributed by Eppinger and Hess, Pottinger, Brown, and many other observers in this country and abroad. Though the subject is still far from precise, a perusal of the writings of these men and clinical observation lead one to expect many revelations in the near future regarding the relationship of the vegetative nervous system to Graves' disease.

The autonomic or vegetative nervous system consists of two balancing mechanisms, each holding a check over the other: (1) the *sympathetic* nervous system which governs the accelerating endocrine organs and is concerned with catabolic processes, converting the reserves of the body by the mobilization of bodily sugar, and (2) the *parasympathetic* or vagal nervous system which governs the inhibiting endocrine glands and is concerned in anabolism or building up of reserves, especially the storing up of bodily sugar.

Brown thus sums up the relation of the sympathetic nervous system to the endocrine organs: "Designed as an intensive preparation for action or defense, the sympathetic response may be so dissociated, perverted, or prolonged as to produce through the thyroid gland Graves'

disease with its danger to life, through the pituitary body, diabetes insipidus with its attendant discomforts, through the pancreas and other endocrine glands, excessive mobilization of the blood-sugar, which is the first stage of the metabolic disorder that culminates in diabetes; it may disorganize digestion by exciting spasm and atony in stomach and bowels, and inhibiting the secretion of the digestive juices; it may keep blood pressure at a level which is inappropriate for the task of the heart and the arteries. These effects are not necessarily distinct—thus, intestinal stasis from sympathetic inhibition causes poisons of putrefactive origin to be observed, which in their turn lead to vasoconstriction, and hence an unduly raised blood-pressure." Again, the author's explanation of the rôle of the sympathetic in loss of balance of carbohydrate tolerance is especially lucid: "(1) Sympathetic stimulation increases blood-sugar as a defensive measure. (2) Sympathetic stimulation causes increased secretion of adrenals, thyroid, and pituitary. (3) Vagus stimulation excites secretion of the pancreas; the antagonism between its internal and external secretions does not mean an antagonistic nervous supply; it means a diversion of nervous energy from one channel to another. (4) The general effect of sympathetic stimulation is katabolic, and mobilization of blood-sugar is a preparation for katabolic action. (5) Therefore the sympathetic both by increasing the secretion of glands which diminish carbohydrate tolerance and by inhibiting the gland which increases carbohydrate tolerance, would raise the blood-sugar above the leak-point, and glycosuria would result."

Thus, depending upon which division of the vegetative nervous system dominates the individual in a series of symptoms, the conditions known as *sympatheticotonia* on the one hand and *vagotonia* on the other are recognized. Sympatheticotonia is produced either by stimulation of the sympathetic, inhibition of the vagus, or both. Contrariwise, vagotonia is produced by stimulation of the vagus, inhibition of the sympathetic, or both. Vagotonia is due mainly to endocrine dysfunction and to toxemia, especially of intestinal origin.

If due to vagal stimulation, vagotonia may be overcome by atropin; if produced by sympathetic inhibition, adrenalin is the remedy of choice. Thus, for example, the use of adrenalin enemas in the vagotonic diarrhea of exophthalmic goiter is very successful in overcoming this distressing symptom. Pilocarpin and eserin, on the other hand, are vagal or parasympathetic stimulants. Hence, a diagnosis of vagotonia or of sympatheticotonia can be made by therapeutic tests. Vagotonic symptoms are improved by adrenalin and atropin and are aggravated by eserin and pilocarpin. Sympatheticotonic symptoms are aggravated by atropin and adrenalin and relieved by eserin and pilocarpin.

It is especially in exophthalmic goiter that the terms sympatheti-

cotonia and vagotonia are applied, because groups of symptoms lend themselves to assignment under one or the other heading predominantly. Ideally speaking, the symptoms referable to sympatheticotonia and vagotonia, respectively, may be conveniently tabulated as follows:

SYMPATHETICOTONIA

1. Tachycardia and subjective heart symptoms.
2. Marked exophthalmos and dilated pupils.
3. Moebius sign; epinephrin mydriasis.
4. Dry eyes.
5. No hyperidrosis.
6. No diarrhea nor bladder irritability.
7. No hyperchlorhydria.
8. No eosinophilia.
9. No respiratory arrhythmia.
10. Rise in temperature.
11. Falling out of hair.
12. Reduction in carbohydrate tolerance.

VAGOTONIA (PARASYMPATHETICOTONIA)

1. Relatively slight increase in heart rate; no subjective heart symptoms.
2. Relatively slight exophthalmos and contracted pupils.
3. Marked von Graefe sign and wide palpebral fissure.
4. Eyes excessively moist.
5. Hyperidrosis.
6. Diarrhea and bladder irritability.
7. Hyperchlorhydria.
8. Eosinophilia.
9. Respiratory arrhythmia.
10. No rise in temperature.
11. No falling out of hair.
12. No reduction in carbohydrate tolerance.

An attempt carefully to check up these supposed clinical findings of sympatheticotonia and vagotonia in a given patient will yield many apparent inconsistencies, so that a classification of disease, especially exophthalmic goiter, on this basis, can be made in a relative sense only. The fact is that in Graves' disease there is a confusing combination of both sympatheticotonia and vagotonia in which, in the average instance, sympatheticotonia seems to predominate over one group of complaints and vagotonia over another, without either division of the vegetative nervous system gaining complete control over a clinical situation. However, I am not in accord with the extremists of the reverse school who flout the existence of these terms as entities, and who claim that there is no such thing as sympatheticotonia and vagotonia. We must assume a midway position, accepting what we actually see in our clinical work, namely, that the sympathetic nervous system does play a definite rôle in some patients and the parasympathetic in others, and that in most cases of Graves' disease there is a definitely recognizable combination of the two. Future open-minded observation and experimentation will clear up some of the prevailing ambiguities which abound in matters pertaining to the vegetative nervous system.

THE OCULO-CARDIAC REFLEX

The Oculo-Cardiac Reflex (Dagnini-Aschner phenomenon) is a procedure wherein, in normal persons, there is a slowing of the heart of

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from 5 to 13 beats per minute following compression of the eyes. An *exaggerated oculo-cardiac reflex* occurs when the heart is slowed more than 13 beats per minute, and it is *diminished* when the rate is reduced less than 5 beats per minute. An *acceleration* of the heart rate when the eyes are compressed constitutes an *inverted oculo-cardiac reflex*. This phenomenon has been accredited with a varying degree of importance in the determination of sympatheticotonia and vagotonia, and in the diagnosis and prognosis of exophthalmic goiter. In vagotonia the reflex is exaggerated; in sympatheticotonia it is either diminished or inverted.

Parisot, Richard, and Simonin, experimenting on rabbits, offer the following data: In the normal rabbit, compression of the eye causes a slowing of the pulse, varying with the subject, from 3 to 20 pulsations. A single intravenous injection of 0.5 gm. of thyroid extract causes an exaggeration of the reflex. After a series of 10 subcutaneous injections in 20 days, the reflex is very much less or slightly inverted. After thyroidectomy there is an exaggeration of the reflex followed in 10 seconds by a secondary acceleration of the pulse for 30 seconds or more. The same is true for incomplete thyroidectomy. In thyroidectomized animals, compression 30 seconds after the intravenous injection of 0.5 gm. thyroid extract causes a slowing of the pulse, but less marked than the preceding; the secondary phase of acceleration is not marked. Injection of adrenalin suppresses or inverts the oculo-cardiac reflex during the phase of excitation of the sympathetic, but the reflex reappears slightly after return of the blood pressure and pulse to normal.

Blanc reports the result of observation of the oculo-cardiac reflex in the psychoneuroses and in thyroid dysfunction. In hypothyroidism when pressure is made on the eyeball there is a greater slowing of the heart than normal; on the other hand, in hyperthyroidism the decrease in heart rate is not excessive. Occasionally after thyroid medication the result is "negative," i.e., instead of slowing of the heart there occurs acceleration. This is taken to indicate an excessive irritability of the sympathetic system.

Marañon, testing the diagnostic and prognostic value of this sign in 47 cases of all types of hyperthyroidism of varying severity, states that no relation could be established between symptomatology or severity of the disease and the character of the reflex. Marañon therefore regards the test as useless either for diagnosis, prognosis, or as determining treatment.

Mosler and Werlich warn that the oculo-cardiac reflex and similar physical tests of the excitability of the vegetative system must not be relied on too implicitly.

Espino remarks that the extensive literature on this subject contains so much that is contradictory that it is difficult to estimate the significance of this reflex. He applied the test to 35 inmates of an

institution for the insane, each tested 3 times. In these psychopaths the response to compression of the eyeball was a moderate slowing of the pulse and respiration. This reaction was never intense, and in a few instances there was no reaction, or the pulse and respiration were speeded up instead of slowed. The response varied at different times in the same individual, even in the course of the same day.

An experimental and comparative study was made by Naccarati of groups of normal and pathologic subjects. He found that this reflex is subject to individual differences and variations, as is the pulse. He states that since normal persons are subject to the same changes in their oculo-cardiac reflex, it cannot constitute a positive sign for differential diagnosis. It may serve only as an indicator of probability. The classification of the oculo-cardiac reflex into normal, abolished, inverted and exaggerated classes cannot be accepted on account of the extreme inconstancy of the reflex index: the same normal or abnormal subject may present a positive, a negative, and a zero index at different times, even when the hour, position, and the amount of ocular compression are kept constant. About 40 percent. of the normal subjects examined by Naccarati showed a reflex index of from 0 to plus 4.

From the deductions of these and other observers, including my own observations, it would appear that though the oculo-cardiac reflex is a very interesting phenomenon, it does not at present assist us materially in diagnosis and prognosis of Graves' disease or other affections. It is highly probable, however, that when we are in possession of more precise information of the physiology and pathology of the vegetative nervous system, we shall find the oculo-cardiac and allied phenomena valuable clinical assets.

MISCELLANEOUS DIRECT METABOLIC SYMPTOMS

Fatigability and Weakness.—Lack of physical and mental strength or endurance is one of the constant evidences of the disease. The patient is quickly tired out, and there is a physical inability to cope with the daily duties. The college student cannot keep up with his class, and, despite the leaps and spurts evincing brief periods of concentration, there is no reserve of strength to sustain it. Thus the depression of disappointment following lack of accomplishment is added to fatigability. The housewife cannot perform her daily duties, neglecting her household and children through sheer force of physical circumstances. The business man finds himself losing ground in his race with his competitors and soon traces this to personal incapacity. The workingman is discharged by his employer for not being up to the mark in productive ability, which latter may be associated with certain mental eccentricities which render him discordant with his fel-

low workers. Thus, in brief, the subject of Graves' disease is an individual undergoing a process of progressive unfitness.

Frequently there is a giving way of the legs and the patient falls as though suddenly paralyzed. The duration of these spells may vary from a few minutes to an hour or two. This may become a very troublesome phenomenon, and occurring at most unexpected moments or places, is capable of causing considerable embarrassment to the patient.

Loss of Weight accompanies and is the most important cause of weakness. From the very rapid loss in weight occurring in the fortunately rare instances of acute Graves' disease to the very slow but persistent loss associated with the usual or chronic form of the affection, many gradations are seen. For instance, a patient whose normal standard of weight is 150 pounds, if afflicted with the usual form of Graves' disease, may find himself losing at the rate of 5 to 10 pounds a month during the first 3 months, after which the loss becomes more gradual, until at the end of 6 or 7 months following the appearance of the frank manifestations of the disease, the weight may be reduced to somewhere between 100 and 110 pounds, at which point it will remain with greater or lesser constancy. During all this time, the appetite may be excessive, resembling in this respect the voracious hunger of diabetes mellitus. The catabolic processes dominate metabolism so completely that despite an intake of more than the normal amount of food for the individual in question, the loss in weight is continuous. When the minimum weight is reached, however, the increased ingestion of food seems to meet the metabolic demands sufficiently to prevent further emaciation, for a smaller body does not require as much nutriment for its maintenance as the formerly large body, and the catabolic processes are now sufficiently fed by the abnormally increased food intake. An apparent paradox is occasionally seen when a patient suffering with all the evidences of a typical syndrome of the affection, including a high basal metabolism, appears to possess an excess in weight. A careful investigation, however, will show that prior to the onset of the disease the patient was really quite obese, and that the present weight, though above normal, represents a considerable loss since the inception of the disease. In course of time, however, if the progress of the disease is not checked, this patient, too, will become emaciated.

Increased Temperature, with or without sensations of heat or flushes, is quite common, though inconstant. This is due to a quickening of metabolic processes. In the acute form of the disease there may be hyperpyrexia, the fever occasionally rising to 110° F. as in a case reported by Rendu. Ordinarily the rise in temperature is never great; it varies between $\frac{1}{2}$ and $1\frac{1}{2}$ degrees above normal, occurring usually toward the evening. This is seen mostly during the active

stages of the affection, and during physical and mental excitation, restlessness in sleep, and menstruation. At all times, even during favorable progress, these patients are greatly tolerant to cold and intolerant to heat. They look forward to winter months, but dread the summer. Indeed, I have often dreaded the summer months myself, for I find treatment of these patients in warm weather a most trying task.

Augmentation in Height is occasionally described as associated with Graves' disease. Cases have been described by Holmgren, Gram, and many others. It is my view that such patients are usually preadolescent subjects who are undergoing physiological growth and who, afflicted with Graves' disease and its associated quickening of metabolic processes, are seen to pass through a rather aggravated increase in height, often exceeding the height of the parents within several months. The course of the disease is more difficult to check during this growing period, but the maximum height having been reached, therapeutic measures are productive of excellent results. It is possible that hypophyseal overactivity is partially responsible for the undue skeletal growth in these patients.

Diminished Carbohydrate Tolerance is mentioned elsewhere and is probably due to pancreatic, suprarenal, hypophyseal and liver, as well as thyroid involvement. From a mild, almost inconspicuous glycosuria and hyperglycemia, it may become so marked as to resemble diabetes mellitus. Ordinarily, however, this is not a serious problem, and does not interfere materially with dietary management of the disease. It is often a question in my mind whether diminished carbohydrate tolerance is not partially responsible for the loss in weight, excessive hunger and thirst, polyuria, some of the skin symptoms, neuritis, and other symptoms associated with Graves' disease.

Symptoms of Pluriglandular Involvement, though implied throughout the symptomatology of Graves' disease, are more directly in evidence in some patients than in others. For instance, pituitary participation is indicated by such symptoms as diarrhea, glycosuria, irritability, insomnia, miscarriages, and in rare instances, acromegalic features, which latter may result from an overcompensation of the hypophysis in prolonged cases. The *pancreas* is seen to be directly involved, at least functionally, in the presence of hyperglycemia and glycosuria. The *suprarenals* are evidently implicated when it is observed that the patient is covered with cloasmic patches and that there are instances in which the Graves' syndrome and typical Addison's disease are seen in the same patient. Many reports of this association are found in literature. Raymond, for instance, reports the case of a combination of Addison's and Graves' disease in a soldier of 26 years. It is probable that the extreme weakness and low blood pressure commonly observed in Graves' disease are partially produced by suprarenal deficiency. *Ovarian* hypo-activity is indicated by the commonly observed

amenorrhea, sterility, miscarriages, and associated evidences of genital dysfunction. The *parathyroids* have been thought to be in a state of hypofunction, thereby being responsible for the trembling of the body. The *thymus*, because it is commonly hyperplastic, is blamed for such symptoms as tachycardia, mental excitability, dyspnea, and other evidences of the syndrome of Graves' disease. The *pineal gland*, and even the *liver*, *kidneys*, and other organs of doubtful endocrine physiology have been drawn into the net of speculative pathogenesis to explain the cause and symptomatology of Graves' disease.

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CHAPTER XV

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF EXOPHTHALMIC GOITER

TYPICAL exophthalmic goiter is described in the chapter on Symptomatology. In the presence of the four cardinal symptoms, *i.e.*, tachycardia, tremor, enlarged thyroid and exophthalmos, there is no disease in the domain of medicine that is diagnosed with greater ease than Graves' disease. Even the layman knows that exophthalmos and goiter mean exophthalmic goiter. On the other hand, in the absence of bulging eyes and large neck, there is no disease that is more difficult to diagnose. Within recent years we are realizing that there are more cases of Graves' disease in our midst than were ever suspected. This is due to the fact that great numbers of atypical forms of the affection were heretofore unrecognized and therefore misdiagnosed. Early and aberrant Graves' disease, because of an absence of distinct exophthalmos and goiter, were frequently treated for various other afflictions presenting a few clinical features in common with the Graves' syndrome. We must therefore be on our guard, for Graves' disease, because of its varied and widespread symptomatology, is capable of resembling a greater number of other affections than any other disease known to medicine.

The textbooks of medicine are partly responsible for some of the confusion in diagnosis. In most volumes the definition of Graves' disease includes distinct exophthalmos and goiter as essential to diagnosis. Another error is the inclusion of the term hyperthyroidism as a synonym of this disease; this is an implication of the precise etiology of the disease when, in truth, there is still very much to be learned regarding its pathogenesis. Hyperthyroidism, though a probable constituent of the syndrome of Graves' disease, is not the *cause* of the affection, but *incident* to the widespread pathogenesis and clinical manifestations. All efforts to produce Graves' disease artificially through the administration of thyroid substance have failed. The administration of large doses of thyroid extract, though capable of producing hyperthyroidism, is incapable of producing Graves' disease in the normal subject.

The Constant Signs of Exophthalmic Goiter.—From deductions based upon a study of many hundreds of Graves' disease patients, it appears to me that the most constant and reliable evidences of the

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affection in a patient without appreciable exophthalmos and thyroid enlargement are the following, in the order of their importance:

1. Afebrile heart hurry of over 90 per minute, continuous throughout the day and night, little or not at all influenced by the administration of digitalis.
2. A basal metabolism of over plus 15.
3. Emotional disturbances with a reduction of the threshold of emotional response and a quickening of mental activity.
4. Fine tremor of the outstretched fingers.
5. Dermographia and a varying degree of hyperhidrosis.
6. A relative immunity to cinchonism.
7. Weakness, especially of the lower limbs, and unrefreshing sleep.
8. Loss in weight, despite a normal or excessive appetite.
9. Dyspnea on exertion.

The first six above enumerated, when coexistent, are typically characteristic of Graves' disease in the modern conception of the affection, and in combination are present in no other disease.

Typical Exophthalmic Goiter has already been amply described under symptomatology.

Atypical Exophthalmic Goiter is deserving of our keenest attention, for a patient without exophthalmos and goiter may not reach the doctor until marked myocardial degeneration has occurred, when treatment may be futile.

It is occasionally asserted that the patients without exophthalmos and without goiter are not really suffering with Graves' disease but with some other affection. It might just as well be stated that a patient with a central pneumonia is not suffering with pneumonia but with some other disease, simply because the physical signs are not typical; likewise that typhoid fever without rose spots and with an unusual temperature curve is not typhoid.

A large percentage of patients primarily without exophthalmos and goiter may present one, the other, or both signs rather late in the disease. An early diagnosis and the institution of prompt treatment in these patients may avert the onset of these signs.

In view of the consensus of opinion that exophthalmos in Graves' disease is due to stimulation of the cervical sympathetic, it is reasonable to assume that the absence of exophthalmos can be explained by the fact that the cervical sympathetic is not sufficiently stimulated to yield proptosis. There is really no dividing line between the absence and presence of exophthalmos, and what may be regarded by one clinician as slight exophthalmos may be ignored by another. Even the exophthalmometer is of no practical assistance in borderline or doubtful cases. Again, in most patients classified as not having exophthalmos, the eyes may be unduly brilliant, especially on attention, and in nearly all there is either a typical or a larval von Graefe's sign to be

elicited. Moreover, in a percentage of patients there is definite exophthalmos in one eye, while the other appears normal.

The absence of thyroid enlargement in a given patient may be explained on the ground that an organ may be in a state of dysfunction or hyperfunction without apparent enlargement for a while, or the organ may never enlarge perceptibly. However, in almost all patients classified as not having goiter, there is a definite enlargement perceptible on palpation. Here, too, the personal equation of the diagnostician is a factor, for the term goiter is an elastic one, and in doubtful cases what is goiter to one clinician may be regarded as normal by another. In nearly all patients without goiter, the typical bruit over



FIG. 78.—Exophthalmic goiter without exophthalmos.



FIG. 79.—Exophthalmic goiter without goiter.

the thyroid may be elicited on auscultation. Aside from the absence of exophthalmos and goiter in a goodly percentage of patients, there are those who present goiter without exophthalmos, others who present exophthalmos without goiter, and still others who present unilateral exophthalmos. Again, we might observe a swelling of but a portion of the thyroid, the remainder of the organ being apparently normal. And though we expect all patients to appear emaciated, there are some whose weight is normal and others who are indeed obese from the overcompensation through the great intake of food by those who were corpulent at the outset. The atypical case of the disease, then, is not at all exceptional in the experience of those who devote much time to a study of these patients.

There are forms of Graves' disease whose departure from the typical is not necessarily dependent upon the presence or absence of exophthalmos and goiter. For instance, in the course of events in a subject of Graves' disease, not only are we frequently confronted with atypical symptoms in the form of a predominance of sympatheticotonia over vagotonia, and *vice versa*, but often we find a confusion even greater, namely, an alternation or a combination of hyperthyroidism and hypothyroidism in the same individual.

In the average atypical case of Graves' disease the *constant* evidences of the syndrome are otherwise practically the same as in a case presenting the usual exophthalmos and thyroid swelling. The basal metabolism, tachycardia, tremor, restlessness, weakness, emaciation, dermographia, and other features present no marked differences. It is evident, however, that without exophthalmos the usual physiognomy of frozen fright is absent; the expression is rather one of anxiety or helplessness. In patients without apparent thyroid swelling the pulse is less labile, and they are more apt to present an abnormally high blood pressure.

DIFFERENTIAL DIAGNOSIS OF EXOPHTHALMIC GOITER

As already implied, exophthalmic goiter or Graves' disease may mimic a greater number of affections commonly met with in practice than any morbid process in the domain of medicine. Let us now mention the most usual conditions which possess clinical symptoms in common with Graves' disease.

Toxic Adenoma is the most important condition requiring differentiation from exophthalmic goiter. To Plummer is due the credit for having called attention to marked and clear-cut differences between the two conditions. Though it was well known that exophthalmic goiter is a distinct entity and that toxic adenoma, often termed "secondary Basedow" or "Basedowified" goiter possesses many points in common with exophthalmic goiter, it was also known that there are many distinct points of difference. Plummer for the first time presented in concise form the distinct differences separating the two conditions with precision. It is these two, exophthalmic goiter and toxic adenoma, that are most often confused one with the other by the general practitioner, much to the detriment of the patient, for exophthalmic goiter is a *nonsurgical* condition with a widespread etiology, while toxic adenoma is a *surgical* condition with an etiology of local nature. The following tabulated differential points will assist the general practitioner in the diagnosis of these conditions:

TOXIC ADENOMA

(Hyperthyroidism, Secondary Toxic Goiter, "Basedowified" Goiter.)

1. Patient is usually of middle age.
2. Goiter present years before onset of symptoms.
3. Goiter is essentially adenomatous, often nodular in shape, and usually large, nonpulsating, noncompressible, without thrill or bruit.
4. Exophthalmos and expression of chronic fright rare; no eye signs.
5. Tachycardia not extreme, often materially influenced by sleep and digitalis.
6. Hypertension and myocardial degeneration common.
7. Tremor often absent; if present, is coarse and atypical.
8. Mental symptoms relatively mild.
9. No tendency to gastrointestinal crises.
10. Dermographia often absent; when present, is not intense.
11. Loss in weight comparatively slow.
12. Symptoms may be produced in a normal person by administration of thyroid extract or thyroxin.
13. Surgical interference with the thyroid eminently successful; usually no recurrences or regeneration, as mass is encapsulated.

EXOPHTHALMIC GOITER

(Graves' Disease, Basedow's Disease, Parry's Disease, Flajani's Disease, Hyperplastic Goiter, Dysthyroidism.)

- Patient is usually a young adult. Goiter often absent; if present, is of recent occurrence.
- Goiter is essentially hyperplastic in nature, rarely large, usually a symmetrical fullness, often pulsating, compressible, and presents thrill and bruit.
- Exophthalmos and expression of chronic fright with characteristic eye signs are usually present.
- Tachycardia more pronounced, not materially influenced by sleep and digitalis.
- Hypotension common; myocardial degeneration may occur late in the disease.
- Tremor nearly always present and typical.
- Mental symptoms relatively prominent, with occasional major psychoses.
- Tendency to gastrointestinal crises.
- Dermographia constant and usually intense.
- Loss in weight comparatively rapid.
- Syndrome not produced by administration of thyroid extract or thyroxin unless predisposition exists.
- Surgical interference with the thyroid a questionable procedure; recurrence because of regeneration is common, as the mass is unencapsulated.

It will be noticed that toxic adenoma has, in common with exophthalmic goiter, an enlarged thyroid, increased basal metabolism, wasting, nervousness, weakness, heart hurry, and often dermographia and tremor.

Nontoxic Goiter.—A patient suffering from simple or nontoxic goiter, appearing in the office of her physician, may present some of the earmarks of apparent toxicity such as apprehensiveness, slightly staring eyes, heart hurry, and even a cold, clammy skin; the patient

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is "scared to death" at the mere thought of an operation, and her symptoms must be construed as psychic in nature, to disappear when she leaves the doctor's office. This, indeed, is neither a case of toxic adenoma nor of Graves' disease.

In general, the differential diagnosis between simple or nontoxic goiter and exophthalmic goiter may thus be stated:

SIMPLE OR NONTOXIC GOITER

1. Frequently a history of goitrous geographical location, heredity or numerous pregnancies, not dependent upon shock or neurotic tendencies.
2. Tendency to distinct circumscription, often assuming markedly noticeable proportions.
3. Comparatively slow growth.
4. Pressure symptoms common.
5. Rarely compressible and tender on palpation.
6. No pulsation, thrill or bruit.
7. No weakness or emaciation.
8. Unless intrathoracic, no cardiovascular, nervous, ocular, gastrointestinal, cutaneous, or urinary manifestations.
9. No change in thymus.
10. Often improved by administration of thyroid extract or the iodids.
11. Quinin test negative.
12. No increased basal metabolism.

EXOPHTHALMIC GOITER

History of nervous shock, fright or a neurotic tendency.

Enlargement is diffuse, smooth, round, often a mere thyroid fullness, rarely assuming a size perceptible at a distance.

Comparatively rapid growth.

Pressure symptoms rare.

Usually compressible and tender on palpation.

Pulsation, thrill and bruit characteristic.

Marked weakness and emaciation.

Characteristic cardiovascular, nervous, ocular, gastrointestinal, cutaneous and urinary symptoms.

Thymus enlargement common.

Symptoms markedly aggravated by thyroid extract and often by the iodids.

Quinin test positive.

Increased basal metabolism.

Nontoxic Goiter with Graves' Disease.—In the presence of the etiological factors, a patient with a simple or nontoxic goiter is quite as likely to manifest the syndrome of genuine Graves' disease as a nongoitrous individual. Such a patient is an instance of nontoxic goiter plus Graves' disease, in which the pre-existing thyroid growth bears no etiological relation to the syndrome; this is therefore not a case of toxic adenoma.

Nontoxic Goiter with Nervousness.—A patient with simple or non-toxic goiter, as well as anyone else, may happen to suffer with neurasthenia, or just so-called nervousness. These patients must also be observed carefully lest we err in diagnosis.

Hypothyroidism or myxedema presents a syndrome in many respects quite the reverse from that of Graves' disease. Since in some instances the two conditions appear in the same patient alternately

or concomitantly, and since myxedema may follow Graves' disease, it is not superfluous to append the following differential tabulation:

GRAVES' DISEASE	MYXEDEMA
1. Usually an enlargement of the thyroid.	Usually no enlargement of the thyroid unless symptoms are secondary to a goitrous condition.
2. Alert expression, facies indicating a degree of perpetual anxiety or fright.	Expression is blank, stupid and bloated.
3. Insomnia.	Somnolence.
4. Increased nervous excitability; flow of thought and speech accelerated.	Diminished nervous excitability; flow of thought and speech sluggish.
5. Marked progressive emaciation.	Gradual increase in weight.
6. Skin moist and soft, dermographia; no mucinous infiltration of subcutaneous tissues.	Skin dry, harsh, puffy, scaly; mucinous infiltration of subcutaneous tissues.
7. Hair not much altered.	Hair becomes thick, brittle and sparse.
8. Temperature somewhat above normal.	Temperature somewhat below normal.
9. Often glycosuria and polyuria.	No glycosuria or polyuria.
10. Tachycardia and vascular throbbing.	Pulse slower than normal, often bradycardia; no vascular throbbing.
11. Exophthalmos and the various eye signs (von Graefe's, Dalmryple's, Stellwag's, Moebius', etc.).	No exophthalmos or diagnostic eye signs. Eyelids puffy and palpebral fissures narrow.
12. Increased respiratory rate with diminished expansion.	Respiratory rate often diminished.
13. Tremor of outstretched fingers, toes, and often of whole body.	No tremors.
14. Gastrointestinal functions hyperactive; appetite normal or increased; symptoms of nervous indigestion and diarrhea may occur.	Gastrointestinal activity sluggish; poor appetite and digestion; constipation.
15. Basal metabolism increased.	Basal metabolism reduced.
16. Symptoms aggravated by thyroid extract.	Symptoms improved by thyroid extract.
17. Quinin test positive.	Quinin test negative.

Effort Syndrome, in common with Graves' disease, presents emotional disturbances, nervousness, weakness, loss in weight, and occasionally heart hurry. But in this condition the thyroid is not swollen, the eyes and basal metabolism are negative, the heart rate is normal during sleep, and many other clinical features present in Graves' disease are here absent. It must be emphasized, however, that a consid-

erable number of cases diagnosed as effort syndrome are really instances of early or atypical Graves' disease.

Shell Shock and Neurocirculatory Asthenia are terms employed during the World War for conditions not clearly understood, but a considerable number of cases so diagnosed sooner or later developed a high basal metabolism, hyperplastic thyroid, exophthalmos and other significant evidences of exophthalmic goiter.

Hysteria, Neurasthenia and Hystero-Neurasthenia present, in common with exophthalmic goiter, such symptoms as emotional disturbances, weakness, heart hurry, digestive disturbances, and occasionally hyperidrosis and dermographia. These may be forerunners of or may accompany Graves' disease. In some instances it may become a difficult problem to make an accurate diagnosis. Juarros among others calls attention to the increasing number of patients diagnosed as hysteria who, in reality, prove to be instances of hyperthyroidism or of Graves' disease. To label every patient who complains of nervous symptoms as a case of hysteria or neurasthenia, as is often done in busy out-patient clinics, is to deprive a large number of Graves' disease patients of the advantage of prompt treatment. The spells of crying on the slightest provocation, the stubbornness, the change in disposition and the varying likes and dislikes, the palpitation, tremor, and staring of the eyes are, of course, common to both hysteria and Graves' disease. But in primary uncomplicated cases the diagnosis should be apparent after a period of careful analysis of the history and symptomatology. The tachycardia of exophthalmic goiter is constant, awake or asleep; the tremor is constant and typical; the thyroid is full and tender; and the diagnostic eye signs are obtainable. This is not true of neurasthenia, hysteria or of hystero-neurasthenia. In the main, it may be said that the neurasthenic assumes an intensely egotistic or introspective attitude unlike the subject of Graves' disease who is alert and quick-minded. In neurasthenia the apparent flushing of the skin due to vasomotor ataxia is uncommon; this is constant in Graves' disease. Laboratory data are of course valuable aids in discrimination.

Nervous Indigestion is often the diagnosis made in the early forms of exophthalmic goiter because of the nausea, vomiting, epigastric tenderness, pyrosis and general abdominal discomfort so frequently occurring as prominent symptoms in the Graves' syndrome. Here a therapeutic regimen calculated to overcome the subjective symptoms fails, and the medical attendant is perplexed as to what next to do for the patient. The difficulty is overcome by attention to details in history taking, physical examination and laboratory data.

Paroxysmal Tachycardia is differentiated in the chapter on the Circulatory System.

Angina Pectoris is rarely confused with Graves' disease. Although

anginoid pains severe enough to resemble angina pectoris may occur in advanced cases of Graves' disease because of the tumultuous action of the heart, a state of unmistakable angina is rare and need not give us much concern. It must be remembered that anginoid cardiac symptoms may occur through pressure on the thoracic vessels by an intra-thoracic goiter as an evidence of mechanical goiter heart. In angina pectoris there is a history of such etiologic factors as syphilis, alcoholism, a hereditary tendency to circulatory diseases, plumbism, rheumatism, and the like; there is an abnormally high blood pressure, fibrosis of the blood vessels, the attacks occurring in paroxysms with the sensation of impending death (the heart rate often being quite normal during that time), and an absence of the cardinal symptoms of exophthalmic goiter.

Addison's Disease may precede, accompany or follow exophthalmic goiter in isolated instances, and often this is so striking that we cannot help being impressed with the apparent relationship between the two diseases, and the physiologic dependency between the thyroid and the suprarenals. Moreover, patches of pigmentation of undoubtedly adrenal origin are frequently observed in otherwise typical instances of Graves' disease. It is for these reasons that occasionally some difficulties arise in differentiating the two afflictions. Careful attention to details in the history, symptomatology, and laboratory data, will render the diagnosis clear.

Pulmonary Tuberculosis is frequently thought of in the presence of the gradual loss in weight, hyperidrosis, rise in afternoon temperature, increased pulse rate, increased basal metabolism, weakness, and diminished respiratory expansion, all of which occur also in Graves' disease. It must be emphasized that a combination of pulmonary tuberculosis and Graves' disease in the same patient is not uncommon. In 17 percent. of 3,000 tuberculosis patients, Janowsky found symptoms suggesting exophthalmic goiter. In 10 percent. the evidences of the syndrome had preceded all symptoms of the tuberculosis by a few months to two years. In another 10 percent. the tuberculosis lesion in the lung had long persisted in a latent phase until the onset of the Graves' syndrome, and this had whipped up the pulmonary process. Even the slightest infection with tuberculosis seems to be enough to sensitize the nervous system so that any physical or emotional stress, intercurrent infection, abortion, parturition or an operation may be followed by symptoms suggesting exophthalmic goiter. Sergent is another observer who is convinced of the presence of a relation between the two conditions. In every tuberculosis suspect the thyroid should be investigated, and the lungs in every case of Graves' disease. In Janowsky's series of cases women were affected about ten times more than men. The variations in temperature, sweats, and other significant symptoms had not been heeded, and the lungs had been examined only perfunctorily,

if at all. In 90 percent, the pulmonary lesions were minimal, with every prospect of a cure under appropriate medical treatment. In general, the differential diagnosis between Graves' disease and pulmonary tuberculosis may be tabulated as follows:

PULMONARY TUBERCULOSIS	EXOPHTHALMIC GOITER
1. No thyroid fullness, tremor, nor eye signs.	Thyroid fullness, tremor and eye signs.
2. Usually a history of exposure to the disease directly or indirectly; or a tuberculous family history.	Not so. Frequently a history of nervous shock or neuropathic tendency.
3. Cough, expectoration, vague chest pains and often Koch's bacillus in the sputum. Tuberculin reaction. Characteristic physical signs over the lungs.	Not so.
4. X-ray examination reveals pulmonary lesions.	X-ray examination may reveal enlarged thymus and dilated heart.
5. Basal metabolism moderately increased.	Basal metabolism markedly increased.
6. Quinin test negative.	Quinin test positive.

Symptomatic Anemia resulting from toxemia and its widespread effects on the vital body processes is present in all cases of advanced Graves' disease. Because of the vasomotor ataxia, the blood impoverishment may not be evident on inspection, the patient often appearing flushed. It is only by means of a blood analysis that we can determine the degree of anemia present. The conclusion that the patient is suffering from "anemia and a run down system" must be guarded against.

Septic Endocarditis is sometimes thought of when the symptoms of Graves' disease are acute. In the presence of a delirious heart, marked prostration, sweating, feverishness, and great weakness, it becomes a rather difficult matter to rule out septic endocarditis. A careful history will usually reveal in the latter case the presence of a preexisting infection, such as acute articular rheumatism, lobar pneumonia, scarlet fever, typhoid, erysipelas, etc. There is marked pain over the abdomen and elsewhere, evidences of embolic processes, scanty febrile urine, frequent chills, leucocytosis, the frequent presence of septic organisms in the blood, early cardiac murmurs, rapid onset of the typhoid state, and an absence of signs and symptoms characterizing exophthalmic goiter.

That **malignant hypertension** may in its clinical manifestations simulate exophthalmic goiter is well illustrated by the following recent case: Mrs. E., age 45, whose chief complaints, beginning a few years ago, consist essentially of throbbing in the neck, dyspnea, palpitation, and weakness. A few months ago a surgeon advised immediate thyroidec-

tomy on a diagnosis of "toxic goiter" based upon a supposed basal metabolism of plus 30, swollen, pulsating thyroid, tachycardia, nervousness and tremor. *Physical examination* revealed a totally normal thyroid gland. The patient being moderately obese, especially about the neck, the adipose tissue in the thyroid area was throbbing violently because of the extreme pulsation and dilation of the aortic arch, right subclavian artery, right internal carotid artery and other vessels about the neck. The heart was rather large, and its rate 120 per minute. The systolic blood pressure was 262 mm.! Laboratory tests relative to thyroid hypersecretion were negative. My immediate diagnosis of malignant hypertension was confirmed by a subsequent two weeks' study of the patient in a representative institution.

The **Psychoses**, as **Melancholia**, **Acute Mania**, **Dementia Praecox**, and the like, frequently enter into the symptomatology of Graves' disease. An atypical Graves' disease (and indeed a typical one as well) may show an accentuation of mental symptoms, for in each patient the most vulnerable part of the body suffers most, and in these instances the psychic area is the seat of crisis. Not only do we frequently observe in the various asylums a percentage of inmates who present the earmarks of Graves' disease, but the very first startling symptom of primary Graves' disease may assert itself in the accentuation of emotionalism, ambitions, and heightened cerebration closely resembling dementia praecox, paranoia, and other major psychoses. Occasionally, a sudden outburst of maniacal delirium or acute dementia may precede the other outspoken evidences of the Graves' syndrome. The lesson to be drawn is obviously the importance of a painstaking physical as well as mental examination in all patients asked to be committed to an asylum, with a view to ruling out Graves' disease.

Spinal Disease, especially paraplegia, is occasionally thought of when a patient with Graves' disease finds his legs suddenly give way from under him while on the street and is obliged to be taken to a hospital in a state of apparent paralysis. Within a half hour or so, however, the patient is again able to walk as before. This symptom occurs more often in men than in women, and is most commonly prevalent in those instances of Graves' disease in which the patient complains bitterly of weakness in the legs.

Biliary Disease.—A case recently came to my attention in a young woman after she had been operated on for cholelithiasis. At operation the biliary tract was discovered to be entirely normal. A more intensive examination of the patient proved her to be an undiagnosed case of atypical Graves' disease.

Acute Appendicitis.—Not only does atypical Graves' disease present crises which are concentrated upon the biliary tract as in the instance just mentioned, but the same may occur in the gut, more especially at the right iliac fossa, closely simulating an attack of acute

appendicitis. Operation in a case of this sort may not only be a useless procedure but may accentuate the Graves' syndrome through surgical shock. Careful efforts at diagnosis will obviate such errors. Rarely, *renal colic* may likewise be simulated in the symptomatology of Graves' disease.

Diabetes Mellitus and its relationship to Graves' disease is a topic which has been discussed very widely during the past several years. The frequency with which glycosuria occurs in Graves' disease, the hyperglycemia, the marked wasting of the body, polyuria, fatty stools and occasional hunger and thirst,—all these and many more phenomena occur in both conditions. It is no wonder, then, that a diagnosis of diabetes mellitus is made when the above symptoms are prominent. Moreover, diabetes presents an increased basal metabolism; it may actually coexist with exophthalmic goiter, gain the upper hand, and in rare instances, the patient may die in diabetic coma. The coexistence of exophthalmic goiter and diabetes mellitus has been noted for a long time. In 1867, Dimonptallier described a combination of this sort in a young woman. Since then many observers, eminently Holst, Denis, Morris, Sainton and Schulman, and others have reported similar clinical pictures. That diabetes mellitus is usually secondary or consequent upon the appearance of exophthalmic goiter in instances where the two coexist in the same patient is attested by the experience of Edmunds, Bergstrand, Friedman and Gottesman, and my own observations. Bergstrand reports the discovery in three of six diabetics of distinct pathologic changes in the thyroid, analogous to those found in exophthalmic goiter. Friedman and Gottesman, in an excellent study on dogs, draw the following conclusions:

(a) The low sugar tolerance in all cases of hyperthyroidism suggests that the islands of Langerhans in this disease are always functionally affected, and that occasionally, histologic changes in them may occur in those rare cases in which exophthalmic goiter and diabetes mellitus are combined.

(b) Since overactivity of the thyroid caused by pathologic alteration in the gland upsets the pancreatic islets, a pathologic condition of the latter may functionally affect the thyroid.

(c) The fact that true myxedematous individuals are not liable to become diabetic, and that a spontaneous cure from diabetes mellitus may occur through hypoplasia of the thyroid brought about by various causes, is highly suggestive that complete removal of the thyroid in man might have a curative effect for the malady.

(d) It is therefore suggested that complete thyroidectomy should be tried in the diabetes of children and in severe diabetes of adults who do not respond to the modern treatment.

Of course due thought must be given to the *rationale* of thyroidectomy as a cure of diabetes mellitus in man, since the cure is worse than

the disease. The question of causal relationship in the presence of exophthalmic goiter and diabetes mellitus cannot be answered with certainty. Labb   reports 5 cases which confirm the possibility of diabetes of thyroid origin. In a series of experiments on rabbits, at times thyroid treatment reduced the capacity for sugar combustion, at other times it increased it; in others thyroidectomy had a similarly variable effect. The hyperthyroidism exaggerates the nitrogen metabolism, and this explains the special tendency to acidosis. There are many observers who believe that there is a thyroidal diabetes mellitus or rather a diabetes depending for its genesis upon Graves' disease. Be that as it may, one thing seems certain: Graves' disease, diabetes mellitus, and such conditions as Raynaud's disease, bronchial asthma, essential epilepsy, arthritis deformans, and a few other affections largely of unknown pathogenesis may exist in the same family and present strong hereditary tendencies. In other words, the family history of a patient with Graves' disease commonly presents evidences in one or more members of one or more of the above mentioned diseases.

For diagnostic purposes in general it may be stated that the absence in true diabetes mellitus of thyroid fullness, tachycardia, exophthalmos, tremor, moist, clammy skin, rise in temperature, emotional disturbances, very high basal metabolism, and a tolerance to quinin, and, on the other hand, the absence in Graves' disease of *persistent* large quantities of sugar in the urine, very large output of urine, great hunger and thirst, dry skin, and visual disturbances, will assist in differentiating the two conditions.

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CHAPTER XVI

DIAGNOSTIC TESTS IN EXOPHTHALMIC GOITER AND HYPERTHYROIDISM

IN observation of the patient suspected of suffering with exophthalmic goiter, the physician should obtain as careful a history as possible, making as detailed a physical examination as he is capable of, and endeavor to dismiss temporarily the idea of laboratory tests. Having arrived at a tentative or even probable diagnosis, laboratory tests, if desirable, may be of service. Tests consistent with the situation in question (not unmindful of the patient's pocketbook) may now be performed to confirm deductions. In the vast majority of instances the trained clinical diagnostician finds that the laboratory tests of a given case are merely corroborative. Tests are occasionally taken too seriously. Sir James Mackenzie has well remarked that "while we may have a hundred new ways of investigating disease in the living, it must also be recognized that we have a hundred new ways of going astray." In this connection Billings' remarks are noteworthy: "With due regard for the value and need of all the splendid ultrascientific laboratory and instrumental methods of physical and functional diagnosis in investigatory medical work, they are needed in the routine clinical care of not to exceed 20 percent. of all the patients of any urban or rural community. Unfortunately, many lay people have been made to believe and apparently a large number of physicians think that the routine application of the ultra-scientific methods of diagnosis is necessary in the majority of cases. The fact is that the diagnosis can be made in fully 80 percent. of all cases by a resourceful general practitioner who will efficiently use his brain, special senses, hands, and an always available simple and inexpensive laboratory and instrumental equipment. In a discussion of the means of diagnosis available to the general practitioner, the history of the past and present condition of the patient is one of the most important, if not the most essential, factor."

The more apparently dependable the test, the more will a percentage of busy practitioners be prone to minimize the value of their own clinical experiences, permitting their senses to become obtunded. Laboratory tests serve their highest purpose when employed as *supplements* to the diagnosis derived from the conscientious use of the senses. Thus a test may *confirm* diagnosis. It is especially in Graves' disease that tests *per se* should be taken with the proverbial grain of salt, for the diagnosis

of endocrin dysfunction is perhaps the most elusive in the practice of medicine, depending largely upon the experience of the clinician. Laboratory tests may be found most useful in determining the severity of the disease and the progress made by the patient as a result of treatment.

It is important to bear in mind that laboratory tests as a rule do not distinguish between toxic adenoma and exophthalmic goiter. In other words, they serve as a rule to confirm the presence of thyroid hypersecretion; the question of whether the thyroid hyperactivity is associated with the Graves' syndrome must be answered by the physician through his diagnostic acumen.

GOETSCH ADRENALIN TEST

This test depends upon the hypersensitiveness of subjects of thyroid hyperactivity to injections of epinephrin, and was described by Dr. Emil Goetsch in 1918. Dr. Goetsch thus describes his test: "The patient should preferably be put to rest in bed at least a day previously. This is particularly desirable in nervous individuals. . . . Having become acquainted with the attending physician or intern who is to do the test, the patient is assured that the examination is in no way painful or dangerous. . . . In some cases reclining for an hour or two in a quiet room is sufficient, when it is inconvenient to have the patient at rest for twenty-four hours previous to the test. Two or three readings are taken, at five-minute intervals, of the blood pressure, systolic and diastolic, pulse rate and respiration. These readings should be fairly constant. If they are not, time should be allowed for the patient to become quite calm. A note is then made in regard to the presence or absence of the subjective or objective condition of the patient. This includes the subjective nervous manifestations, throbbing of the precordium, abdominal aorta or peripheral large arteries, heat and cold sensations, asthenia, and the objective signs, such as pallor or flushing of the hands and face, the size of the pupils, annoying throbbing of the neck vessels and precordium, tremor, temperature of the hands and feet, perspiration and any other characteristic signs or symptoms noticed. The presence or absence of these signs is noted previous to the injection of the epinephrin so that comparison may be made after the injection. A hypodermic syringe armed with a fine needle which, when inserted, causes little discomfort, is then used to inject deep subcutaneously, 0.5 e.c. (7.5 minims) of the commercial 1:1000 solution of 'adrenalin chlorid' into the deltoid region. . . . Readings of the pulse, blood pressure and respirations and any changes in the subjective and objective manifestations are then noted every two and a half minutes for ten minutes, then every five minutes up to one hour, and then every ten minutes for half an hour longer. At the end of one and one-half hours the reaction has usually entirely passed off, sometimes

earlier. The oft-repeated early readings are made in order not to miss certain reactions on the part of the pulse and blood pressure that may come on in less than five minutes after the injection is made. This is particularly true of cases of active hyperthyroidism. In a so-called positive reaction there is usually an early rise in systolic and a fall in diastolic blood pressures. In a very mild reaction the fall in diastolic pressure may occur alone. There is a rise in pulse rate of at least 10 and sometimes as much as 50 per minute. In the course of 30 to 35 minutes there is a moderate fall of the pulse and blood pressure, then a characteristic secondary slight rise and then a second fall to the normal in about one and a half hours. Together with these changes one sees an exaggeration of the clinical picture of Graves' disease or hyperthyroidism brought out, especially the nervous manifestations. The symptoms of which the patient has complained are usually increased and often symptoms which are latent at the time of examination, but which have previously been present are characteristically brought out. Thus, for example, in numerous instances I have noted extra systoles of which the patients themselves are aware at the time of the test and as having been present on previous occasions, doubtless times of clinical exacerbation in their disease. There is often increased tremor, apprehension, throbbing, asthenia, and, in fact, an increase of any of the symptoms of which the patient may have complained, and there may be manifestations of symptoms latent previously to the injection and characteristic of the hyperthyroidism syndrome. Vasomotor changes are common and quite characteristic. Thus, an early pallor of the face, lips and fingers, due to vasoconstriction, is common, to be followed in 30 minutes to an hour by the stage of vasodilation with consequent flushing, sweating and warmth of the face, hands and feet. The respiration at first becomes slower and deeper, even sighing in character, and later more shallow and somewhat more rapid. Yawning is common; in fact, patients in a number of instances have fallen asleep during the test. They may complain of considerable fatigue. . . . In order to interpret a test as positive I have regarded it as necessary to have a majority of these signs and symptoms definitely brought out or increased. Thus there is at times a considerable exacerbation of the objective signs and symptoms, or there may be an increase of 10 points in the pulse and blood pressure together with a moderate increase of symptoms and signs; or, again, there may be only slight changes in pulse and blood pressure and considerable change in signs and symptoms. Any combination of this kind may be regarded as positive. One must not, as has been done by some, regard a test as negative because there has not resulted from the epinephrin injection an increase or manifestation of all the possible signs and symptoms, for, in order to gain a correct interpretation, one must consider the entire clinical picture produced, just as in the disease itself one cannot expect

every one of the characteristic signs and symptoms to be present in order to make a diagnosis."

There has been considerable interest in the value of the adrenalin test since its introduction by Goetsch. Formerly regarded as extremely useful, adrenalin hypersensitiveness is now recognized as indicating *adrenalin hypersensitivity*, a peculiarity of many persons, both normal and abnormal, not necessarily suffering with hyperthyroidism. Moreover, many miscellaneous diseases present a typical positive reaction and often we observe a case of hyperthyroidism with a negative reaction. Let us see what some other observers have to say regarding this test:

Frazier and Wilson obtained positive reactions in men with irritable hearts, in whom the thyroid was not in a state of hyperfunction.

Garnier and Bloch report the application of the Goetsch test to 48 patients. Out of the group 16 gave a definitely positive reaction, 10 gave a weakly positive reaction, and 22 were negative. Among the cases which failed to react were 3 with Basedow's disease, and 2 with myxedema.

Lueders, in a study of methods to enable a discrimination of borderline cases of hyperthyroidism from functional cardiac disorders, concludes that the epinephrin test does not prove diagnostic of hyperthyroidism. Dowden arrives at the same conclusion.

Sandiford, and Boothby and Sandiford conclude that there is not sufficient physiologic basis for the assumption that the reaction of the subcutaneous injection of an active principle of the suprarenal gland is indicative in clinical medicine of activity of the thyroid gland.

Peabody, Sturgis, Tompkins, and Wearn state that a study of the adrenalin reaction in normal individuals showed that it was not present in any of the group of 26 seasoned soldiers; it was present in 14 percent. of 28 medical students and in 48 percent. of 103 soldiers without evidence of organic disease, but with the symptom complex of "effort syndrome." Seven psychoneurotics all gave "positive" reactions. Among hospital patients it was found that 17 percent. of 17 patients with organic heart disease and 57 percent. of 21 patients convalescent from acute infection gave "positive" reactions. Positive reactions to epinephrin were found in 15 out of 21 cases of hyperthyroidism. Six unquestionable cases with metabolism within 21 to 35 percent. above normal gave "negative" reactions.

Russell, Millet, and Bowen, in a study of functional thyroid tests as an aid to differential diagnosis, arrive at essentially the same conclusions.

Lieb, Hyman, and Kessel, as a result of a series of observations, conclude that the epinephrin sensitization test is independent of the ductless glands and is not a specific hormone effect but a physio-chemical change involving the myoneural junctions of the thoracico-lumbar ganglion.

Van Wagonen, who conducted Goetsch tests on a group of students in the Department of Physical Education at Cornell University, states

that "a more physically fit, more symptomless group could not have been desired." Yet in 50 persons comprising it there were 10 positive reactions, or 20 percent., judged by the characteristic changes in blood pressure, pulse rate, general symptoms, and local reactions attending the intramuscular injection of the conventional test dose of epinephrin hydrochlorid.

Many other opinions could be cited to indicate that the discovery of a state of hypersensitiveness to adrenalin injections is of little value in the diagnosis of hyperthyroidism.

My own experience with the adrenalin test leads to the following conclusions:

1. A "positive" reaction indicates that the individual possesses a *hypersensitiveness to adrenalin*, not necessarily hyperthyroidism.
2. It is therefore not a reliable diagnostic test for thyroid function.
3. Since this test, in common with the thyroid extract test, depends for a positive reaction upon an aggravation of existing symptoms or a flaring up of a dormant syndrome, it is therefore, in common with the thyroid extract test, not to be recommended.

THE BASAL METABOLISM TEST

Basal metabolism determinations have become the rule in all diseases in which metabolic changes occur, the calorimeter being related to metabolism as the thermometer to fever. The ideal metabolic equilibrium is represented by 0, indicating a normal relation between anabolism and catabolism. An increase of anabolism over catabolism increases the minus figure, depending upon the intensity of the causal agencies. On the other hand, depending upon the excess of catabolism over anabolism a plus determination is found. It is the concensus of opinion that during normal conditions the basal metabolism may vary between -10 or -12 and +10 or +12. Complete repose during starvation is the condition most liable to yield a cipher reading. In health, during rest of body, mind, and digestive organs, the metabolism bears a practically constant relation to the surface area, "the rafe thereby becoming mechanically a function of the body surface, while in many diseases metabolism is fundamentally deranged, the basal metabolic rate ranging far above or below normal." (Snell, Ford, and Rowntree.)

Physiological Variations.—Basal metabolism is modified by such physiological conditions as age, sex, digestion, rest, activity, menstruation, and other factors. DuBois points out that in the male the average normal rate for each age is approximately 8 percent. lower than in the female. It is lowest in the infant, reaches its height in the fifth year, then declines gradually to the termination of life.

During active *digestion* the basal metabolism may rise to 15 percent. above the normal.

During *exercise* or *excitement*, when there is a quickening of the physical or mental functions, the rate is likewise increased to a variable degree.

During *menstruation* there is often a material increase in basal metabolism, as pointed out by Snell, Ford, and Rowntree.

Pathological Variations.—Variations from the normal, with degrees of increased basal metabolism, are seen in the following pathological conditions:

1. Acute febrile conditions, as the exanthemata, acute tonsillitis, rheumatic fever, lobar pneumonia, typhoid, and the like.
2. Chronic infections such as tuberculosis and syphilis.
3. Chronic cardiac and renal affections.
4. Ingestion of caffeine, strychnine, and other drugs.
5. Malignant disease.
6. The anemias, primary and secondary, including the leukemias.
7. Certain distinctly metabolic disturbances as diabetes mellitus, pituitary disease, hyperthyroidism, and Graves' disease.

Boothby is probably correct in his statement that approximately 95 percent. of all abnormally increased basal metabolism rates observed in practice are due to hyperthyroidism. It is in thyroid hyperfunction characterized by overwhelming *afebrile* catabolism that the highest readings are obtainable. Thus, the variations in metabolic determinations in hyperthyroidism (whether due to an adenoma or an element in the syndrome of Graves' disease) is anywhere from +15 to +50 in mild or moderate cases, to +75 or higher in severe cases.

In an aggravated type of Graves' disease, the basal metabolism, rapidity of emaciation, and (barring paroxysmal tachycardia) the pulse rate, are higher than in any other afebrile disease. In Graves' disease the average rate is approximately +15 percent. higher than in toxic adenoma, due to the participation in the syndrome of the other endocrines, especially the pituitary, gonads, and pancreas, and also because of the excessive stimulation of the vegetative nervous system.

With regard to the value of metabolic determinations in Graves' disease, we might say that both merit and fault may attach themselves to their use. The following faults of this test may be mentioned:

1. The basal metabolism observation is reliable only for the time at which it is taken and frequently is a poor index of the actual condition of the patient, unless the test is performed several times under the same conditions, with a view to obtaining an average.
2. The necessary preparation of the patient and frequently the anticipation may lead to a temporary and even prolonged marked aggravation of the existing syndrome. For instance, I have observed in a male subject of exophthalmic goiter a loss of 5 pounds in weight

during a 3 days' stay at a hospital for metabolic tests, the patient remarking: "The cure is worse than the disease." In this case the rate was far in excess of the expected figure, due to mental excitation. Given two patients of equal sex, age, and apparent severity of the disease, the one who had been about on his feet for several weeks or longer prior to the test will present a higher rate than he who has been kept in bed during a like period. Again, variations may occur in the female during menstruation.

3. Numerous errors referable to the technician may occur. Jones, in a recent article, has cleared the vision of those interested in this work. He concludes that there are three widely different sources of error in calorimetric determinations: (a) the test subject, though in normal health, may have a metabolic rate varying several percent., and may coöperate irregularly or not at all in the performance of the test; (b) the technician, who must execute many details and observations beside those pertaining directly to the manipulation of the instrument, and (c) the apparatus itself, which may introduce error, perhaps consistent, perhaps variable, because of its mechanical defects unknown to the operator. In 1920, Jones, while testing out the apparatus bearing his name, made comparisons of its results with those of apparatus of other makes in nearby hospitals and laboratories, and it was then that he discovered the most noteworthy, not to say startling, errors committed in metabolic determinations. For example, in a normal test subject, the metabolic rate was seen to vary from -17 to +90, through various errors, all of which were discovered to be classifiable in the above mentioned groups. On subsequent occasions Jones found this deplorable state of affairs to exist throughout all parts of the country, and aptly states that "any technician who feels that his own results are an exception to this, should see to his own technic in securing *normal readings on known normal subjects* before offering challenge to the proposition." On over one hundred different occasions, Jones witnessed the beginning technic of over one hundred clinicians or their technicians. Not one of them, during their first attempts, came anywhere near the proper handling of the apparatus or of the subject during the period of testing, and it is a constant wonder to him that suits for malpractice are not the rule rather than the exception through the abuse of this most valuable diagnostic aid. For example, on one occasion the technician reported a plus 8 percent. reading on a suspected hyperthyroid patient. The subject was dismissed as a "neuro." Four months later the physician, convinced that some error in the test had been made, ordered the technician to make a second test. This time the reading was plus 58 percent. Soon it was discovered that because of a reading of three minutes and fifty-two seconds, the rate as determined previously should have been reported as plus 35 percent. instead of plus 8 percent. Now, however, the patient was so much worse that radical operation performed two weeks later

eventuated fatally. On another occasion Jones observed a patient nearly asphyxiated during the course of the test because a tank of gas supposedly oxygen but containing nitrous oxide was used.

4. Another fault is the tendency toward hasty conclusions as to the value of a given therapeutic procedure simply because following the procedure there is a temporary marked reduction in basal metabolism which gives both patient and medical attendants a sense of false security. In a recent discussion on the floor of a Philadelphia Medical Society, it was shown diagrammatically that after thyroidectomy in exophthalmic goiter the basal metabolism rate was very much reduced; after x-ray treatment the rate was reduced to a lesser degree, but there was no reduction following the administration of quinin hydrobromid. In this mechanical, categorical, offhand fashion, surgery was glorified as successful, and nonsurgical treatment as a failure, in the therapy of this disease. These patients, in whom the emotional element plays a leading etiological and clinical rôle, were regarded as "cases," the human element was forgotten, and lifeless figures were juggled to the advantage of statistics. We admit that a reduction of some of the secreting thyroid substance, whether through the knife or the x-rays, yields a reduction in basal metabolism in a goodly percentage of "cases"; but this is temporary and is not cure; on the other hand, we refuse to entertain the idea that the casual administration of quinin hydrobromid is synonymous with a rational regimen of nonsurgical measures in the treatment of Graves' disease. Such hasty generalizations as give rise to the aforementioned statistics are responsible for the still prevailing chaotic status of the therapeusis of the disease. A comparison of results of thyroidectomy, on the one hand, with a régime of expertly applied nonsurgical measures, on the other, a year after the discharge of the respective patients, would open the eyes of many good and conscientious surgeons and give them pause. It would reaffirm the opinion elsewhere expressed that many "lumps on the neck" are not indications for surgery.

On the other hand, the following are the chief merits associated with the basal metabolism test in Graves' disease:

(a) It assists in confirmation of the diagnosis in apparent cases *i.e.*, in cases of the disease in which there is little doubt as to the diagnosis.

(b) It is useful in the elucidation of vague cases, *i.e.*, in the differentiation of Graves' disease from phthisis, neurasthenia, hysteria, neurocirculatory asthenia, and even "nervousness" associated with an incidental simple or nontoxic goiter. It must be repeated that only the skill of the clinician, not calorimetry, can discriminate between Graves' disease and toxic adenoma.

(c) It is an index to the severity of the disease.

(d) It is an index to the course and prognosis of the affection and the evaluation of the results of treatment.

In commenting upon these points, it might be stated that the experienced internist who has had a large series of Graves' disease patients under observation has little use for the calorimeter as an asset to his work. Though it is not my purpose to minimize the value of this important laboratory procedure, I feel that aside from its use as a *supplement* in the diagnosis of uncertain or borderline cases, too much reliance is placed upon calorimetric determinations. The general picture of the patient, more especially the pulse rate and weight, is a reliable index to the severity and course of the affection as well as an indication of the result of treatment. Moreover, the pulse rate and weight of the individual are both insusceptible to any considerable error, they may be observed at very frequent intervals without preparation of the patient, it is not necessary to be a laboratory technician to make these observations, and, on the whole, they are strictly dependable.

Relation of Basal Metabolism to Pulse Rate.—Many observers, eminently Stewart, McGuire, Peterson and Walter, Read, Benedict and Murchauser, Sturgis and Tompkins, and others find a striking relationship to exist between basal metabolism determinations and the pulse rate. In my own observations, I find that in the absence of auricular fibrillation, taking 72 as the heart rate in males and 76 in females, with plus 10 as the starting point in calorimetric determinations, the basal metabolism is increased by 10 points with every increase of 12 in the heart rate in males, and 10 points for every increase of 14 in heart rate in females. In common with other observers, I find the pulse rate quite as reliable a guide of the severity and course of the affection as basal metabolism determinations. The pulse rate is also a reliable index of the results of treatment, the rate becoming lower as the patient improves, remaining normal when recovery is reached. In exceptional instances, however, the pulse rate is quite as unreliable a guide as the basal metabolism observations. Thus, in a given patient the basal metabolism may be normal in the presence of a pulse of 90 or more; again, the basal metabolism may be plus 20 or more in the presence of a normal pulse rate. These exceptions may be explained by the patient's individual peculiarities prior to the onset of the illness, such as a congenitally slow or rapid heart, as the case may be. Again, a patient may have recovered from the entire syndrome, except a still persisting heart hurry, which lags alone for still a month or two, despite a normal basal metabolism. Finally, a patient may present a temporary bradycardia on recovery from the disease.

Basal Metabolism Apparatus.—The methods employed in the determination of the basal metabolism rate are two: direct calorimetry, measured in terms of heat combustion, and indirect calorimetry, measured in terms of oxygen combustion. Direct calorimetry requires more elaborate apparatus and greater training than indirect, and is therefore

more applicable to institutions than to the ordinary situations in which patients are found.

There are two methods of indirect calorimetry; the closed circuit or Benedict method, which depends upon the rebreathing of air plus oxygen, the apparatus absorbing the exhaled CO_2 ; the diminution in the volume of oxygen during a given period indicating the quantity of oxygen consumed by the patient. The simplified closed circuit apparatus of Jones and Sanborn are also extensively used. The other is the open circuit method, recommended by Boothby, in which the patient inspires atmospheric air and expires into a gasometer through a series of tubes, mask and valves. A modified gasometer was designed by Bailey. After the total number of

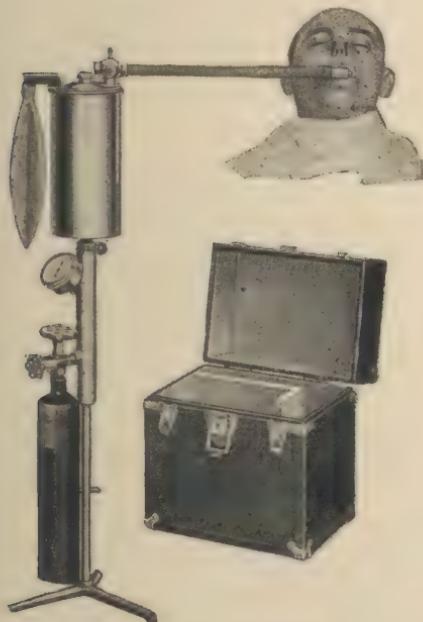


FIG. 80.—The Jones Metabolimeter.

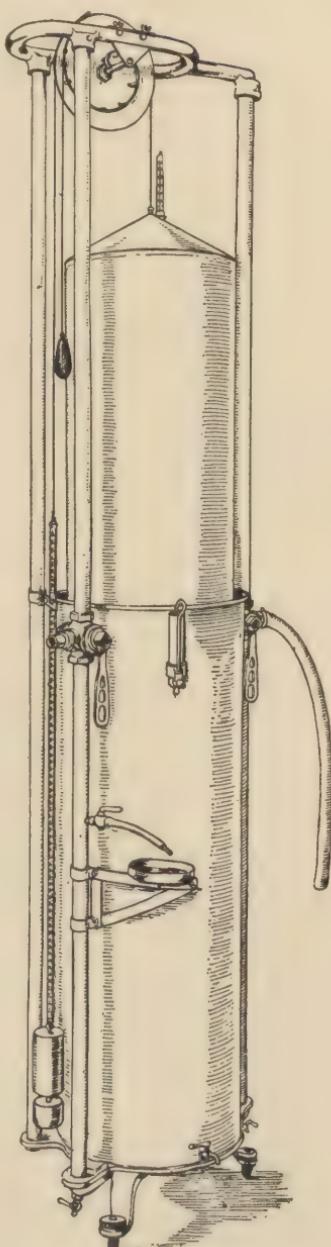


FIG. 81.—Gasometer as designed by Dr. Cameron V. Bailey of the New York Post-Graduate Medical School.

calories produced per hour has been calculated, the technician, with the aid of the DuBois and DuBois formula, can express the calories produced in terms of calories per square meter of body surface per hour. The result is the basal metabolism rate.

As a complete description of clinical calorimetry would mean the writing of a volume on this subject alone, and since the safest technician is he whose contact with patients has taught him how to avoid errors and achieve dependable results, I have refrained from a consideration of the methods of procedure commonly employed in this test.

Conclusions.—1. Basal metabolism tests even under apparent favorable circumstances are open to many errors. The apparatus, the method employed, the patient, and the technician must be properly "checked" if we are to avoid being misguided by the figures.

2. Metabolic tests in Graves' disease should, in the main, serve as a supplement, not a mainstay in diagnosis.

3. This laboratory procedure may serve to differentiate doubtful cases, but we must be conservative in our opinion, for the disease from which Graves' disease is to be differentiated may itself be associated with an increased basal metabolism.

4. The basal metabolism test serves its greatest purpose in the determination of the degree of toxicity in a patient, and in checking up the results of treatment. Though highly useful in this respect, and mindful of its valuable aid in laboratory work, there is a strong tendency on the part of open-minded clinicians to take fewer metabolic determinations in Graves' disease, and give more attention to the weight and heart rate as clinical guides.

THE BRAM QUININ TEST

In 1917, I devised a test for hyperthyroidism which depends upon the singular tolerance of these patients to large doses of quinin. The utility of this diagnostic measure compares very favorably with the other tests herein described, and because of its simplicity and harmlessness in application, it is perhaps the most practicable to the busy practitioner.

The peculiar tolerance to quinin by sufferers from malaria and from such febrile conditions as pneumonia, the acute tonsillar diseases and other infectious processes, must not be construed as a state of natural immunity from the effects of the drug, but as a temporarily altered condition of the bodily reactions, to return to normal on the recovery of the patient. These instances of tolerance are, of course, easily determined and need not detract from the reliability of the quinin test in hyperthyroidism.

The administration of quinin to persons otherwise normal but possessing a susceptibility to its effects, or the administration of large doses

of quinin to average individuals results within from a few hours to a few days in a sensation of fullness and roaring in the head, tinnitus, and impaired hearing, with occasional impaired vision, headache, insomnia, and sometimes hematuria, purpura, erythematous areas and subdermal swellings. At times there is seen a rash which is with difficulty distinguished from that of measles. Where extreme susceptibility exists, even minute doses of quinin give rise to uncomfortable symptoms which, in the average person, would require large doses to produce, though fatal quinin poisoning is practically unknown.

Subjects of thyrotoxemia are exceptionally tolerant to quinin administration during the course of the disease, and occasionally for a varying period of time after recovery. In fact, this toleration to the drug in moderately large doses practically amounts to an immunity. No ample reasons for this phenomenon have been advanced. Is it because the thyroid toxin in the blood exerts a neutralizing or modifying influence on the quinin, depriving the latter of the potentiality for producing the syndrome of symptoms known as cinchonism? Is it the presence of the increased basal metabolism in thyroid toxemia that in some way produces this immunity to cinchonism? Is it because of the peculiar state of vasomotor instability and arterial relaxation in this disease that the drug is so well tolerated and usually taken with advantage? Or is it a combination of these suggested factors that obtains in explanation of this interesting fact? These and perhaps other questions with reference to this phenomenon remain to be answered; meanwhile, observation proves that doses of quinin which would almost invariably produce at least head and ear symptoms in average persons are taken with impunity by patients whose thyroid output is excessive.

The technic of the test is simple. The patient is given a dozen capsules, each containing 10 grains of the neutral hydrobromid of quinin, with instructions to take one capsule 4 times a day, to be washed down by an ample quantity of lukewarm water, *i.e.*, an hour or two after meals and at bed time. Very rarely do we meet with normal persons who can take more than 10 or 20 grains of quinin a day without symptoms. By the time 20, 30, or 40 grains have been taken by persons whose thyroid function is not excessive, there develops a sense of fullness in the head, impaired hearing with tinnitus, often dizziness and headache, and occasionally a feeling of slight gastric and bladder discomfot. Persons possessing a degree of susceptibility or idiosyncrasy will experience these symptoms after the first or second capsule; while those less susceptible may not complain until 60 to 100 grains have been taken. In the presence of a hyperactive thyroid, no symptoms develop from the daily administration of quinin hydrobromid even if given during a period o' weeks or months; on the contrary, improvement in the Graves' syndrome is frequently observed. In these patients, though gastric disturbances may constitute an element in the primary complaints, the

administration of this dosage is apt only occasionally to aggravate the gastric condition slightly. If combined with proper gastric sedatives, however, this objection is overcome.

The hydrobromid is employed because it is the most acceptable of all the quinin salts and may be handled in larger doses without producing extreme discomfort in a patient whose thyroid gland does not functionate excessively. Also, the effects of this drug in negative patients wear off more promptly than other forms of quinin. In the series of cases primarily observed to prove the efficacy of the test, none of the untoward symptoms experienced by non-hyperthyroid patients persisted beyond several days after the discontinuance of the drug.

My first report on the quinin test (*Med. Rec.* [N. Y.], 1920, 98, 887) consisted of results of observations in a series of patients suffering with the following conditions: (a) Nervous indigestion, incipient pulmonary tuberculosis, hysteria, and neurasthenia; (b) simple adenoma of thyroid; (c) cystic goiter; (d) mixed adenomatous and cystic goiter; (e) "goiter heart" (types of b, c, and d, chiefly substernal, with pressure symptoms); (f) malignant goiter (secondary degeneration of simple nontoxic goiter); (g) secondary Basedow or "Basedowified" goiter (toxic adenoma); (h) Basedow "fruste" (early Graves' disease, with or without thyroid swelling); (i) well defined exophthalmic goiter or Graves' disease.

It was found that the least tolerant to quinin administration were those in (a), excepting the patients with incipient pulmonary tuberculosis who were not troubled with head and ear symptoms until after a drachm was taken. The others in (a) were obliged to discontinue somewhere between the taking of the second and the fourth capsules (20 to 40 grains). Patients of class (b), (c), and (d) were able to take on an average of 5 capsules, the individual tolerance varying between 30 and 80 grains. Two showed a mild erythematous rash which disappeared soon after the discontinuance of the drug. Those of class (e) were rather less tolerant to quinin, most of them experiencing headache, tinnitus, and dizziness before the fifth capsule was taken. The two patients in class (f) were rather old, weak, and somewhat feverish, and since they were already complaining of head and ear symptoms due to pressure and induration of the neoplasm, the quinin was discontinued after the administration of the third capsule, and no deductions were made. Patients of classes (g), (h), and (i), 67 in all, each a subject of thyroid toxemia, presented no untoward symptoms after taking the 12 capsules, excepting a slight increase in gastric discomfort in a few who formerly complained of nausea and vomiting. The usual head and ear symptoms were not experienced.

Among those who have tried the quinin test in their thyroid cases are Sainton and Schulman of Paris, and Pfahler of Philadelphia. Pfahler has employed the test both on controls and patients, and reports his

observations as follows: "The quinin-hydrobromid test, recommended by Dr. Bram, seems to have considerable value, and I believe can be used without harm. I have used it in some instances in which the diagnosis was undoubted, and in some cases in which the diagnosis was doubtful. The test seemed to give me satisfactory results. I first tried the test on myself and my associates, and then used it on patients. . . . In the normal person there will be a pronounced cinchonism after the administration of from 2 to 6 or 8 doses, but the hyperthyroid patient can take this continuously for weeks."

Since my primary report on this test in 1920, I have employed it as a routine in all patients and have been able amply to confirm its virtues as an asset in the diagnosis of hyperthyroidism. It is not only associated with a comparatively small percentage of error (approximately 5 per cent.), but practically devoid of harmful effects in "positive" subjects.

The quinin test, when positive, confirms the diagnosis of hyperthyroidism, but, as in the case of other tests, does not distinguish between toxic adenoma and Graves' disease. The test is of marked value in differentiating hyperthyroidism (with or without Graves' disease) from the following, in each of which the test is negative:

- (a) Simple or nontoxic goiter, with or without psychical tachycardia;
- (b) Mechanical goiter heart, a state of heart hurry and disturbance due not to thyroid intoxication, but to mechanical cardiac embarrassment because of pressure from an intrathoracic goiter;
- (c) Incipient pulmonary tuberculosis;
- (d) Neurasthenia, hysteria, nervous indigestion;
- (e) Paroxysmal tachycardia;
- (f) Effort syndrome;
- (g) Diabetes mellitus.

There are many other conditions occasionally confused with hyperthyroidism, in which the test may be employed with advantage. Finally, the quinin test is highly serviceable in arriving at a diagnosis in those instances of Graves' disease in which both goiter and exophthalmos are absent. In such patients a positive quinin test may be regarded as conclusive.

In addition to its value in the diagnosis of thyroid hypersecretion, the test is an indicator of recovery in a large, though as yet unknown percentage of patients. I have found that when a patient who has been able to take 20 or 30 grains of quinin hydrobromid daily for months suddenly begins to complain of characteristic tinnitus aurium this is a most welcome sign of the cessation of thyroid hyperactivity. In other words, *these patients do not complain of tinnitus aurium unless and until all active hyperthyroid or Graves' symptoms have disappeared.* Patients may recover and still possess a relative immunity to cinchonism; possibly these are the instances susceptible to relapse, requiring further observation. But I have observed in a large series

of cases that when a patient formerly insusceptible to cinchonism suddenly becomes sensitive to further quinin administration, and *tinnitus cannot be traced to other causes*, the recovery is a most happy one, and the patient is able to enter the ranks of the active and doing.

To summarize my remarks on this test for thyroid hyperactivity, the following points may be stressed:

1. The quinin test in the diagnosis of hyperthyroidism is associated with less than 5 percent possibility of error; it is therefore at least as reliable as any other test mentioned in this work, both from the viewpoint of "positive" and "negative" results.
2. It is a valuable index to complete recovery of the patient.
3. It is harmless to the patient, does not require elaborate, costly apparatus or expertness in its performance.
4. It is therefore the most practical and dependable test at the disposal of the busy practitioner.

HYPERGLYCEMIA TEST

Hyperglycemia is one of the pathognomonic, though not altogether constant laboratory signs of thyroid hypersecretion. The diminished carbohydrate tolerance evinced by these patients has been known for a long time, and may vary from a mere inconspicuous increase in blood and urinary sugar to findings characteristic of diabetes mellitus. Usually the hyperglycemia is slight or moderate, vacillating with the general clinical picture of the patient, remissions, crises, and other events. Ordinarily, the ingestion of 100 gm. of sugar causes no increase in the normal individual's blood, the sugar content of which is about .085 percent. In hyperthyroidism, the ingestion of this quantity of sugar increases the normal content to about double. The ingestion of larger quantities of the extract of the thyroid gland yields the same result.

McCaskey points out that every reading of over .1 percent. represents a hyperglycemia when tested with a fasting stomach. In discussing this test, McCaskey arrives at the following conclusions: 1. Alimentary hyperglycemia following the ingestion of 100 gms. of glucose is present in probably every case of thyrotoxicosis. 2. It is rarely, if ever, present at the end of the first hour in normal persons, although it may have occurred at the end of about 30 minutes. 3. Its presence, therefore, in one hour, and especially in two hours, always indicates abnormal carbohydrate metabolism unless gastro-intestinal function is delayed. 4. It occurs in latent, and of course in manifest, diabetes, in alcoholism, malignant disease, arthritis, and very probably in a considerable number of infections, acute, sub-acute, or chronic, in the same category with arthritis. 5. Before attaching a positive diagnostic value to alimentary hyperglycemia in suspected hyperthyroid-

ism, these conditions and possibly others of which we are now learning must be excluded. 6. While its positive value can only be considered corroborative, its negative value in excluding hyperthyroidism is very great and probably exceeds 90 percent. 7. In hyperthyroidism there is no constant direct ratio between its intensity and the height of the alimentary hyperglycemia, although in general the blood-sugar values in severe cases are high. 8. Too much importance should not be attached to alimentary blood-sugar values below 140 mgm. of sugar in 100 c.c. blood, although sharp lines of demarcation cannot yet be drawn.

The most satisfactory procedure in the performance of the blood-sugar test is Epstein's modification of Lewis and Benedict's method. The blood is taken before breakfast. Then the patient is given 100 gms. of glucose dissolved in 200-300 c.c. of water. An hour later another specimen of blood is taken, followed by still another at the same interval. These specimens may be taken at half-hour intervals, if desired, 5 or 6 times being required to obtain the necessary findings. Specimens of urine should be taken at the same time for analysis. Normally, the ingestion of 100 gms. of glucose should not yield hyperglycemia within an hour. In instances of hyperthyroidism, the sugar wave reaches its height at the end of the first hour, falling to its lower level in the greater percentage of cases at the termination of the second hour.

The diagnostic and prognostic value of the hyperglycemia test has been the subject of much discussion. McBrayer, in an analysis of 74 cases in which both blood-sugar and basal metabolism tests were performed to differentiate pulmonary tuberculosis from hyperthyroidism, arrives at the following conclusion: "In about one-third of the cases of chronic pulmonary tuberculosis, the basal metabolic rate and the blood sugar are both increased; in about one-fifth of all such cases there may be an increased basal metabolic rate and a normal blood sugar, or just the reverse, while in a much smaller percentage of cases, you may find any change in either basal metabolic rate or blood sugar; very seldom, however, would both be decreased or even one decreased and the other normal. Remembering the well-established fact that hyperthyroidism consistently shows both an increased basal metabolic rate and an increased blood sugar, it is impossible for us to draw from our work any other conclusion than this: The determinations of basal metabolic rate and blood sugar are of no practical value in the differential diagnosis of chronic pulmonary tuberculosis and hyperthyroidism."

Roussy and Cornil conclude that in the hyperglycemia test, only a negative test is really decisive.

Dowden, too, does not believe the sugar tolerance test to be a reliable guide in hyperthyroidism.

In the series of cases studied by Peterson, H'Doubler, Levinson, and Laibé, these observers arrived at the following conclusion: "There was no direct relation disclosed between the extent of the delayed sugar curve and the hyperthyroidism, some of the most marked cases revealing only a slightly or moderately delayed utilization. . . . The sugar tolerance curve as a diagnostic procedure test for hyperthyroidism did not prove very satisfactory in our hands, as it was found to be subject to too many factors, was a hardship on the patient, and required a specially trained laboratory worker."

I can heartily agree with these opinions. The blood-sugar test is a valuable asset to laboratory diagnosis, but in the majority of cases the diagnostic acumen of the physician is sufficient to recognize the affection. All unnecessary laboratory work performed in patients as physically and mentally sensitive as sufferers of Graves' disease are strictly to be avoided as added strain and drain on the already deficient energies of the patient.

MISCELLANEOUS TESTS

The Kottmann Test.—Kottmann, and also Peterson, H'Doubler, Levinson, and Laibé, as well as other observers, call attention to a test devised by Kottmann in the diagnosis of thyroid function. The theoretical premises are, on the basis of previous work of Kottmann, with serum in pregnancy, that certain physio-chemical differences must exist in the serum in cases of thyroid dysfunction, and that the chief difference would exist in the state of dispersion of serum colloids. Because of the peculiar relation of iodin to the glandular metabolism, experiments were carried out with colloidal iodin preparations, using silver iodide because of its well-known photosensitivity. The technique of the test is as follows: To 1 c.c. of clear serum are added 0.25 c.c. of a 0.5 percent. solution of potassium iodide and 0.3 c.c. of a 5 percent. solution of silver nitrate. The resulting suspension of silver iodide in the serum is next exposed for 5 minutes at a distance of 25 cm. to a 500-watt Mazda lamp (or other light of equal intensity). Then 0.5 c.c. of a 0.25 percent. solution of hydroquinon is added and the color changes observed at 5-minute intervals. In carrying out the test a dark room is theoretically desirable, though diffuse daylight does not materially interfere with accurate results. The color reaction that develops after the addition of hydroquinon varies with different serums. With serum from hyperthyroid cases, Kottmann found the original yellowish color of the serum mixture persisted for a considerable time; in normal serums a brown color (silver iodid reduced to free silver) makes its appearance quite promptly; in serums from hypothyroid cases, Kottmann found the development of the brown color reaction accelerated. The serum from individuals who have had

bromides retards the reaction, and such medication must be excluded if the test is to be carried out.

The Kottmann test seems to be a fairly reliable index to thyroid function. Such conditions as malnutrition, hysteria, physical and mental excitation, and occasionally normal serum are apt to yield a positive reaction, but the percentage of error seems relatively small.

The Complement Fixation Test.—Koopman, Berkeley and Koopman, and Berkeley have described a serum fixation test which is both interesting and promising. Koopman finds that the blood of some patients with symptoms of Graves' disease binds complement in the presence of an antigen made from normal glands. To prepare the antigen, Koopman proceeds as follows: The glands of dogs are obtained under aseptic precautions as soon as possible after death. All extraneous tissue is removed and the gland is minced finely with sterile scissors. The mass of thyroid is weighed carefully and is then ground in a mortar with washed, sterilized sand and an amount of sodium chloride equal to one-tenth gram for each gram of gland used. A few drops of 2 percent. trioresol is added for each 10 gms. of thyroid, and the mixture is bottled and kept in the icebox. For use, 10 c.c. of distilled water is used for each gram of gland in the suspension of sand and ground thyroid. The sand and solid matter are removed by centrifugation. A mixture of thyroids from several dogs is recommended. This antigen, which necessarily contains much extraneous matter, deteriorates slowly and after about three weeks it is necessary to secure a new supply. The test is set up in the form of a titration, using a constant amount of the patient's serum, which is not more than one-fourth of the quantity which is anti-complementary. The antigen is used in varied amounts, beginning with an excess and ending with the least amount that can be expected to give fixation of complement. At the same time the anti-complementary titer of the antigen is determined by setting up a series of control tubes containing the same quantities of antigen as used in the test. The result is indicated by the difference between the quantity that binds complement in the presence of serum. A negative serum with antigen will often bind less complement than the antigen alone. A serum is considered positive when it binds complement in the presence of one-half or less than one-half of the anti-complementary dose of antigen, and the smaller the amount of antigen necessary for complete fixation the stronger the reaction. Fixation is carried out for from 4 to 6 hours in the icebox.

Starlinger's Blood Test.—This observer, believing that the blood in passing through the thyroid gland must receive certain qualities, decided that a method of examination embodying this principle would serve to determine the functional activity of the organ. His work proved that in thyroid hyperfunction there is a diminution of fibrino-

gen in the venous blood but that in thyroid hypofunction the reverse occurs. Starting with the theory of Herzfeld and Klinger that fibrinogen represents the first stage in the decomposition of the albumin of an organ, he made refractometric determinations of the fibrinogen content of the arterial and of the venous blood of the thyroid. He tested further the varying sedimentation velocity of the red blood corpuscles, and the results of sodium chlorid flocculation, whereby at the same time a control of the several methods was secured. In only one case out of the 15 under observation was there no difference to be distinguished between the arterial and the venous blood of the thyroid. With the exception noted, all the findings thus far are in complete accord with expectations. For example, in one case the fibrinogen in the blood from the artery totaled 0.65 percent., while it was 0.37 percent. in the blood from the vein; the suspension stability of the erythrocytes averaged respectively 45 and 61, and precipitation was respectively 4 plus and 2 plus.

Parisot and Richard's Thyroid Test.—(*"The Sign of the Thyroid"*) These observers note a considerable slowing of the pulse in patients with hyperthyroidism, following injections of thyroid extract; they therefore conclude that this procedure is useful in the diagnosis of thyroid hyperactivity. The reaction evidently depends on whether the vagus or the sympathetic system happens to be most sensitized at the moment. But one reaction was constant in hyperthyroidism, namely, a pronounced slowing of the pulse by 10 to 30 beats, after the injection of 1 gm. of thyroid extract. They call this "the sign of the thyroid." The systolic blood pressure usually declined also, there being a drop from the maximum of from 20 to 40 m.m., and the oculo-cardiac reflex was exaggerated. They found this test useful in determining or excluding the participation of the thyroid in pluriglandular disturbances. The number of cases studied to date is too few to give this test a definite place in the diagnostic laboratory.

The Thyroid Extract Test, depending upon the flaring up of latent or mild symptoms of thyroid hyperactivity by the administration of thyroid extract, should never be employed. Not only should no test be employed in this affection which depends for a positive reaction upon making the patient worse, but the administration of thyroid gland is apt to lead to disaster. I have seen an exaggeration of exophthalmos to the point of panophthalmitis and an urgent need for eyeball enucleation, resulting from thyroid administration. There are reports, notably those of Musser and of Forchheimer, in which the administration of relatively small doses of thyroid extract in susceptible individuals caused death. The thyroid test is therefore mentioned to be condemned as dangerous.

Hunt's Acetonitrile Test.—When acetonitrile (CH_3CN) is taken into the body, it is converted into hydrocyanic acid, because of meta-

bolic processes. This substance, therefore, is, when ingested, a poison. Certain substances, especially iodin and thyroid extract, are capable of reducing or perhaps preventing the formation of hydrocyanic acid in the body after the ingestion of acetonitrile. In 1905, Hunt, experimenting on mice, found that the feeding of thyroid gland markedly increased the resistance to poisoning by acetonitrile. In 1910 Hunt and Seidell believed that this resistance offered by thyroid extract might serve as a clinical test for hyperthyroidism. The test, however, has not yet successfully materialized. Recently, Miura, experimenting with mice, employed various iodin-containing substances including potassium iodid, di-iodotyrosin, thyroid extract, and thyroxin. He concluded that thyroid extract conferred resistance to poisoning by acetonitrile in direct proportion to the iodin content of the former. Potassium iodid and di-iodotyrosin conferred no protection. Thyroxin gave the greatest resistance to poisoning. It would seem, then, that the active principle conferring immunity to acetonitrile poisoning is really not iodin, but thyroxin, the active principle of the thyroid gland. The test, of course, is still impracticable to apply to human subjects.

Atropin Test.—Somewhat related to the adrenalin test is the so-called atropin test, indicating an increase in responsiveness to hypodermic injections of this drug, which in turn implies an increased tonus of the bulbo-sacral system. This is not a reliable test for the neuro-endoerine dysfunction of Graves' disease, although in the majority of subjects there is a sensitiveness to atropin. The test is carried out as follows: A hypodermic injection of gr. $\frac{1}{150}$ to $\frac{1}{100}$ of atropin sulphate is given the patient and observations of the pulse rate are made every minute or two. In "positive" subjects there is usually a primary stimulation of the vagus center asserting itself in a slowing of the pulse rate within approximately 5 minutes. This is followed by an acceleration within 5 to 10 minutes thereafter, reaching its height in about a half hour. No uncomfortable subjective or objective phenomena are observed, excepting an occasional dryness of the mouth.

The Pituitary Test, originated by Boudouin and Porak, is also employed to detect an excess of thyroid secretion in the blood. One c.c. of an extract of posterior lobe of the pituitary body injected into the patient causes slowing of the pulse within 2 minutes which in Graves' disease passes off in 7 or 8 minutes. In normal persons the pulse is accelerated by this injection, attains its maximum in 5 or 6 minutes, and returns to normal within 15 minutes.

Ascoli and Fagioli call attention to a local phenomenon resulting from subepidermal injections of pituitrin. The reaction is identical with that obtained with a solution of adrenalin of about 1-2,000,000 dilution. There is formed a bluish spot at the site of injection, which is soon surrounded by a white halo, gradually changing to red.

Loewi's Mydriasis Test.—While experimenting with pancreatectomized animals and in human diabetes, Loewi found that the instillation of 1:1000 adrenalin chlorid into the conjunctival sac produces mydriasis within a half hour. This condition attains its maximum within an hour, and remains from 10 to 18 hours. Continuing his experiments, he concluded that the adrenalin stimulates the sympathetic, which in turn dilates the pupil. Accordingly, he soon discovered that in subjects of hyperthyroidism adrenalin produces mydriasis, and is of service as a diagnostic test.

The Digitalis Test.—Insusceptibility to digitalis, already mentioned, is a characteristic of Graves' disease patients, and may be regarded as one of the important means of differentiating the tachycardia of these subjects from the heart hurry of other conditions.

Certain other *blood findings* of variable diagnostic significance, the *oculo-cardiac reflex*, the various *eye signs*, *skin tests* and *urinary findings*, are described in other chapters.

Conclusions.—The real confirmative value of a diagnostic test in Graves' disease (the same may be said of almost any diagnostic test) depends upon how small is the percentage of error associated with the performance of the test. I have included in the description of the most popular laboratory tests the deductions of observers whose minds are open and who are seeking to separate fact from mere opinions. In the perusal of these deductions one is impressed with the danger of confidence in methods outside of trained personal diagnostic acumen, which, after all, should be our fundamental guide. With the exception of basal metabolism determinations and the quinin test, I am convinced (and this conviction is based upon a prolonged experience in a large series of cases) that other laboratory tests, though useful as supplements, are not essential. I feel that the vast majority of cases of Graves' disease, typical as well as atypical, can be diagnosed by the experienced clinician through his senses, with the *occasional* use of reliable tests in doubtful instances.

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CHAPTER XVII

VICIOUS AND THERAPEUTIC CIRCLES IN EXOPHTHALMIC GOITER

THE term "vicious circle," though largely theoretical, always has an attraction for the student of clinical phenomena, fascinating him to the extent of conjuring up circle after circle from a single sign or symptom. Vicious circles may be assumed to exist in all diseases, but it is in exophthalmic goiter especially, with its manifold implications, its universally distributed signs and symptoms, its often uncertain course, and, finally, its varied therapeusis, that circles are most often alluded to as real entities.

As I conceive it, a vicious circle¹ in disease is the term applicable to a clinical situation in which a cause or causes having been productive of an effect, the latter in turn becomes a cause, perpetuating the existence of the former. Thus cause and effect each becomes both cause and effect. It is often impossible to determine which was cause and which effect, as the involved phenomena appear simultaneously and have become interdependent.

The vicious circle in turn implies the possibility of the operation of correcting therapeutic measures, which, antagonizing or breaking through the vicious circularity by remedial agencies, succeed in affecting recovery. In addition, therefore, we might describe certain therapeutic circles, *i.e.*, the favorable or unfavorable result of therapeutic measures on clinical phenomena. A few of these will here be mentioned.

Vicious circles have already been mentioned in a casual way in a few of the chapters in this work. Let us now present the most important of these circles diagrammatically:

¹ It was Dr. Jamieson B. Hurry of Reading, England, who wrote what is probably the first monograph on "Vicious Circles in Disease," and it was this work that impelled me to present my own views on the circles observed in exophthalmic goiter.

ETIOLOGICAL VICIOUS CIRCLES

CIRCLE 1:

Toxemias and Endocrine Dysfunction form a vicious circle which has long been recognized. In a person predisposed to Graves' disease, an infection or autointoxication may serve as the exciting cause of the disease. The disease in turn reducing the patient's resistance, serves to aggravate the degree of causal toxemia, thus completing the circle. The discovery and eradication of the infection, however, is not alone sufficient in treatment, as other morbid processes have already been begun. It is therefore necessary to treat both cause and effect to eradicate the syndrome.

CIRCLE 2:

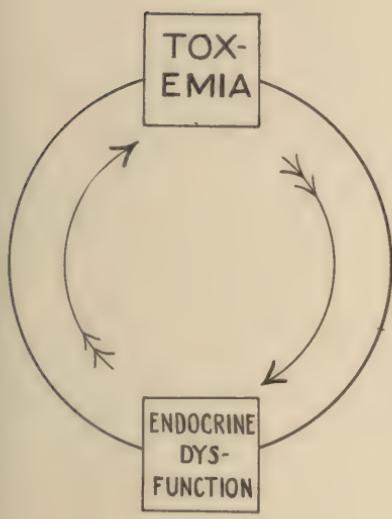
Thyro-adrenal Hyperfunction leads to **Pancreatic Hypofunction**, and the latter, in turn, tends toward the perpetuation of the former. In actual practice the existence of the circle seems confirmed by the carbohydrate intolerance observed in Graves' disease, and the occasional improvement of the thyro-adrenal overactivity often seen following treatment with pancreatin.

CIRCLE 3:

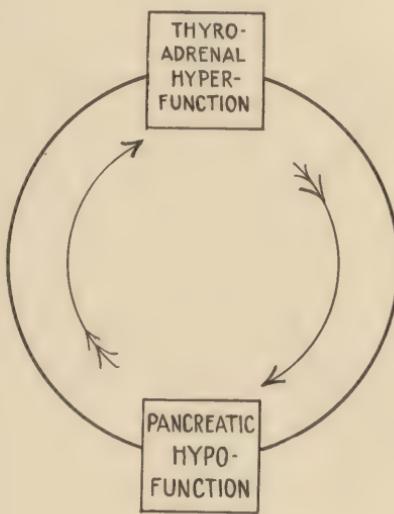
Thyroid Hyperfunction and Ovarian Hypofunction present a well known vicious circle which may occur independently of Graves' disease, but is often observed as a prominent element in the syndrome of this affection. Improvement following the administration of corpus luteum or whole ovarian substance is frequently observed.

CIRCLE 4:

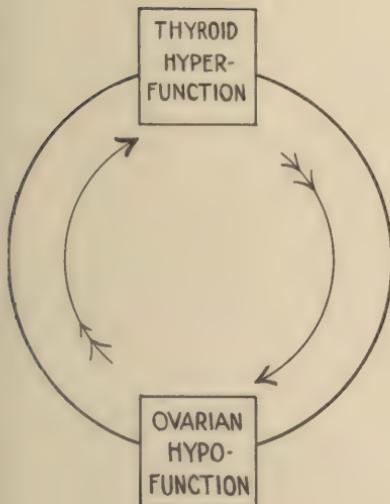
The Thymus stimulates **the Thyroid** and *vice versa*, as evidenced by the presence of a hyperplastic thymus in a large percentage of patients with Graves' disease. Though some advocate the administration of thymus as a remedy in Graves' disease, I have never found it of service. Theoretically, at least, this substance seems contra-indicated. Treatment consists in the institution of a broad management of Graves' disease, when the vicious circle becomes effaced in the course of time.



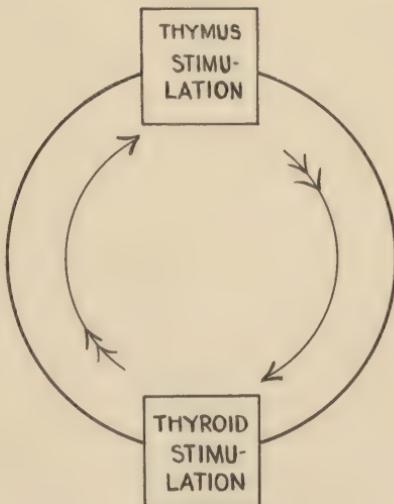
CIRCLE 1.



CIRCLE 2.



CIRCLE 3.



CIRCLE 4.

CIRCLE 5 :

Thyroid and Adrenal Hyperactivity and Sympatheticotonia constitute a vicious circle that is quite evident in the clinical picture of Graves' disease. The thyroid stimulates the adrenals, the adrenals the thyroid, and the sympathetic nervous system is stimulated by and in turn stimulates the thyro-adrenal structures. Which of the triad first made its appearance or whether the entire vicious circle occurred simultaneously it is often difficult to determine. But it matters little, as treatment must be general, directed toward overcoming the entire syndrome by an attack on all conceivable causes and effects.

CIRCLE 6 :

Emotional Excitement and Thyroid Hyperactivity exemplify the recognized influence of mental excitement over thyroid function and *vice versa*. Increased mental activity increases thyroid activity; the latter in turn stimulates mental activity. It matters not where the process is started, whether emotionally or at the thyroid; and, indeed, it is often difficult or impossible to determine which came first, but the reciprocal process having begun, the circle becomes complete. Measures calculated to reduce both the mental excitability and the thyroid hypersecretion are here indicated, not to break, but to efface the circle. If hyperthyroidism is due to *toxic adenoma*, surgery may break the circle and effect cure by thyroidectomy. In thyroid hyperactivity forming a part of the syndrome of Graves' disease, however, the secretion of the organ is curtailed by rest, a non-flesh dietary, quinin, corpus luteum, and other drugs. The cerebral hyperactivity is lowered by rest, a non-flesh dietary, psychotherapy, and such substances as veronal and luminal.

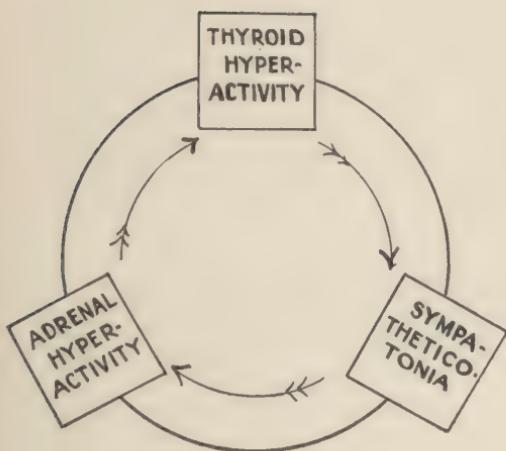
SYMPTOMATIC CIRCLES

CIRCLE 7 :

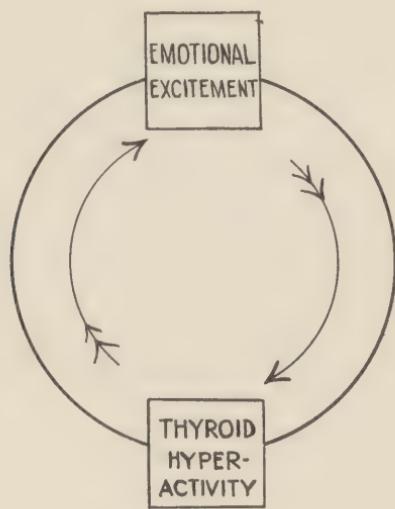
In the male, *sexual excitability*, with *sexual neurasthenia* or *priapism* is due to the quickening influence of the *neuro-endocrine dysfunction*. The latter is in turn aggravated by the sexual excitability. Indeed, in a small percentage of cases this circle is capable of dominating the entire clinical picture of the disease.

CIRCLE 8 :

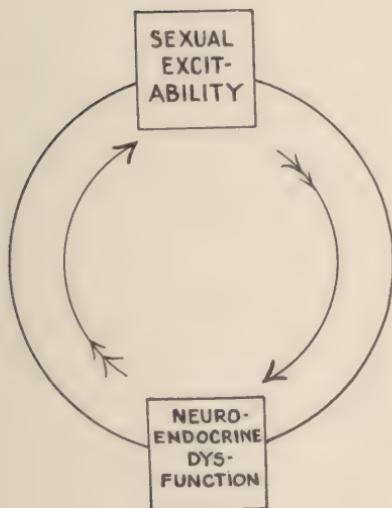
In the female, Graves' disease may render the generative organs so sensitive as to result in *vaginismus*, with consequent dread of coitus. But the desire and libido are nevertheless kept hyperactive through the quickening influence of the syndrome. Thus the ungratified desire in turn leads to an aggravation of the syndrome; the latter in turn increases the vaginismus and dread of coitus. Menstrual disturbances, sterility, and in the event of pregnancy, miscarriage, are the results of this clinical situation. Here, too, the treatment is general.



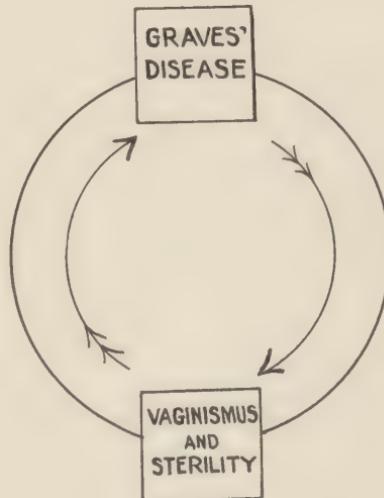
CIRCLE 5.



CIRCLE 6.



CIRCLE 7.



CIRCLE 8.

CIRCLE 9 :

Palpitation and Nervousness.—Palpitation is often a very distressing symptom in Graves' disease, in most cases leading to a notion on the part of the patient that heart disease exists and that there is imminent danger of death. This makes for markedly increased nervousness and apprehension, which latter, in turn, coupled with added introspection, increase palpitation. A remedy or remedies calculated to alleviate palpitation, nervousness, or both, eliminate this important circle from the symptomatology of Graves' disease. Physical and mental repose, psychotherapy, and such drugs as veronal or luminal usually succeed in eradicating the circle.

CIRCLE 10 :

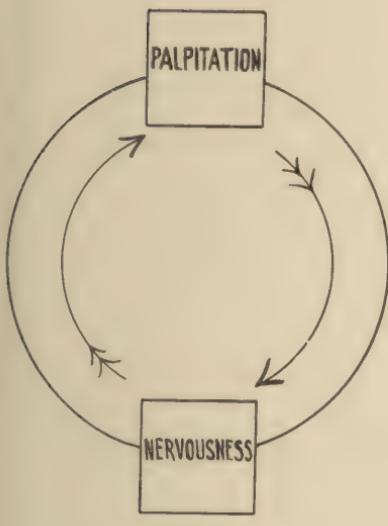
Tachycardia and Emotionalism.—This circle is somewhat similar to the one described in palpitation and nervousness, excepting that tachycardia is mainly objective, while palpitation is subjective. That emotionalism may increase the heart rate is unquestioned; I have frequently seen a heart rate of 100 rise to 140 and more during the sudden recall to the mind of the patient of an unpleasant thought or incident calling forth tears. Tachycardia, in turn, increases emotionalism by cerebral stimulation and hastened cellular exchange in the brain. As direct treatment of tachycardia is unsatisfactory, the management here is general therapeusis of the disease, with special emphasis on psychotherapy as a means of overcoming emotional symptoms.

CIRCLE 11 :

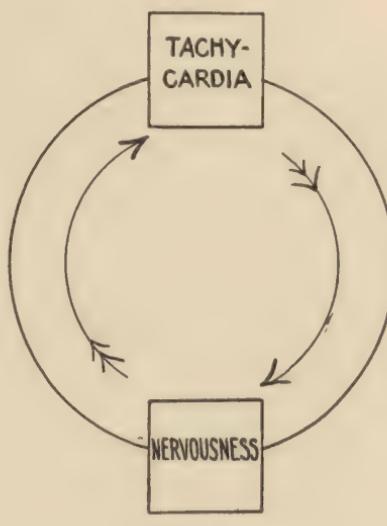
Emotional Symptoms and Nervous Indigestion are both elements of the Graves' syndrome, forming a vicious circle which, if persisting, makes for greater chronicity of the disease. Fear, laerimation, apprehension, hysteria, and the like, aggravate indigestion; the latter, in turn, giving rise to distressing symptoms after eating, aggravates the emotional symptoms, the loss in weight and weakness. Treatment should attack one, preferably both of these factors, and this accomplished, improvement is but a matter of time. Rest, psychotherapy, pleasant environments, sedatives, and antacids are the most effective remedies.

CIRCLE 12 :

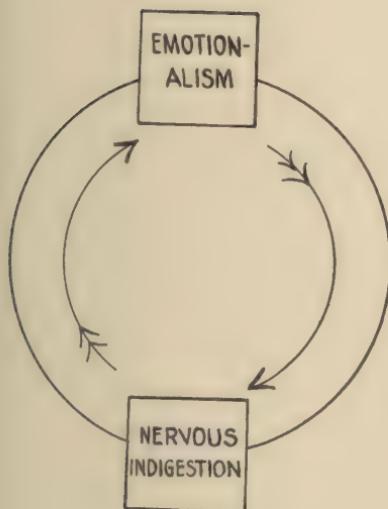
Hyperchlorhydria associated with Graves' disease and **Deficient Food Intake**, forms a vicious circle which must be overcome at once, lest all other measures in treatment are futile. Often in these cases the stomach is not given enough to do, so that the gastric secretion is free to give rise to discomfort, the latter further diminishing appetite, digestion, and food intake. The administration of an antacid (as outlined in the chapter on Diet), and the use of some persuasion in inducing the patient to take more food, especially milk and eggs to take up the acidity, will efface the circle within a few weeks.



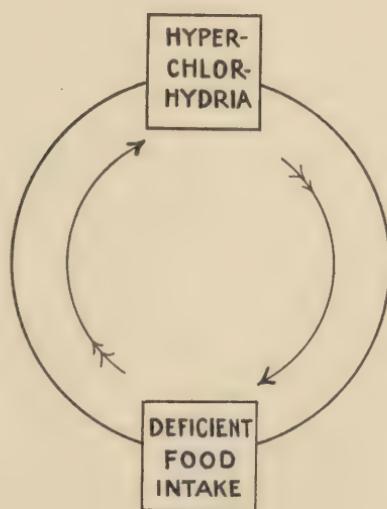
CIRCLE 9.



CIRCLE 10.



CIRCLE 11.



CIRCLE 12.

CIRCLE 13 :

Insomnia and Mental Excitement form a vicious circle which must be eliminated at all hazards, else all other efforts to help the subject of Graves' disease fail in their purpose. Insomnia aggravates mental excitation; the latter aggravates insomnia. It matters not which came first; they are now interdependent. Fortunately, both conditions are easily controlled by psychotherapy and such substances as veronal or luminal. A note of warning must be sounded against the use of opiates, which, if employed, would in course of time lead to disaster.

THERAPEUTIC CIRCLES

CIRCLE 14 :

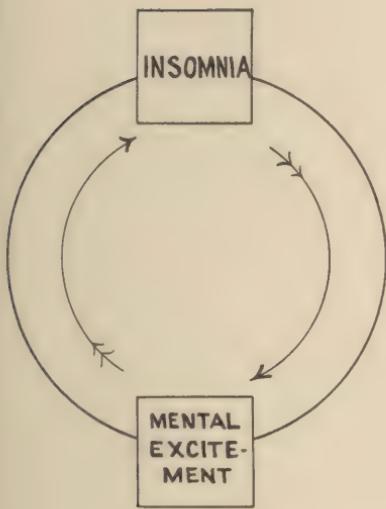
A Flesh Dietary and **Graves' Disease** are interrelated, forming a vicious circle. The animal nitrogenous foods as represented by flesh are recognized as potent stimulants to endocrine dysfunction. The endocrine hormones in turn seem to stimulate a further desire for flesh foods, as is evidenced by the fact that most patients suffering with Graves' disease are very fond of meats. The circle is to be effaced by attacking both sides of the question,—endocrine hyperactivity and the diet. These phases of the question are discussed in other chapters.

CIRCLE 15 :

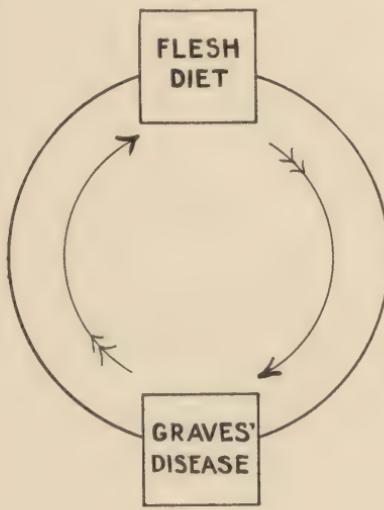
Restricted Diet and **Wasting** are causally interrelated, pointing to the fallacy of the liquid diet and the tendency to treat Graves' disease by starvation and other errors. A restricted diet increases wasting; increased wasting makes it less possible for the patient to take and digest a necessary quantity of food, so that this mode of treatment defeats its purpose and strengthens an already existing vicious circle. The one way to eradicate the circle is to train the patient to forced feeding with a rich diet of non-flesh character.

CIRCLE 16 :

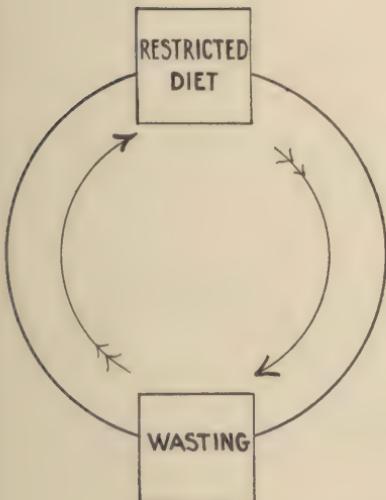
Forced Feeding reduces **Metabolism** and **Wasting**, even as water extinguishes a fire; reduced basal metabolism in turn renders forced feeding more successful. The benevolent therapeutic circle thus established is the most important step in the treatment of Graves' disease, without which any method of treatment is a failure.



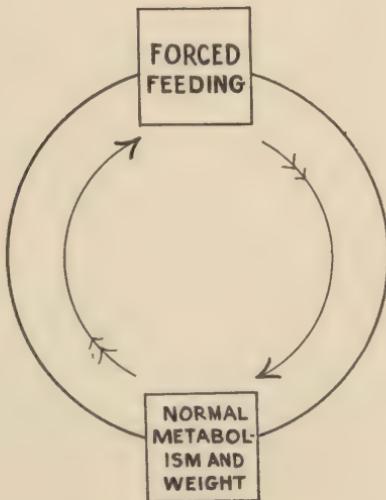
CIRCLE 13.



CIRCLE 14.



CIRCLE 15.



CIRCLE 16.

CIRCLE 17 :

Digitalis Therapy, Indigestion, and Increased Tachycardia are viciously interrelated. The notion in some quarters that the rapid heart of Graves' disease requires digitalis therapy is erroneous, as no amount of this drug can do good during the active stage of the affection. On the contrary, the administration of digitalis further irritates gastric irritability which in turn increases the heart rate, which latter in turn increases intolerance to digitalis. It is obvious that digitalis therapy in the *active stage* of the disease is contra-indicated if we would avoid the above circle as an added strain in the syndrome of the disease.

CIRCLE 18 :

Nonsurgical and Surgical Failure.—Failure of the general practitioner to obtain good results in the treatment of Graves' disease is due to lack of proper study of the patient and lack of individualization in treatment, *not to incurability of the disease by nonsurgical means*. The general attitude of "turn 'em over to the surgeon," without the necessary meditation, is responsible for the ultimate plight of many of these patients. Thus nonsurgical failure leads to an appeal for surgical intervention which in turn fails to cure, since thyroidectomy does not remove the cause of the disease. Nonsurgical methods are now again tried, perhaps with more sincerity, but these are again futile because thyroidectomy has made response to treatment more difficult. Surgery is again resorted to on the grounds of "lack of subtotality" of the primary thyroidectomy. This is a therapeutic vicious circle which in many instances is only effaced by the development of myxedema or the death of the patient.

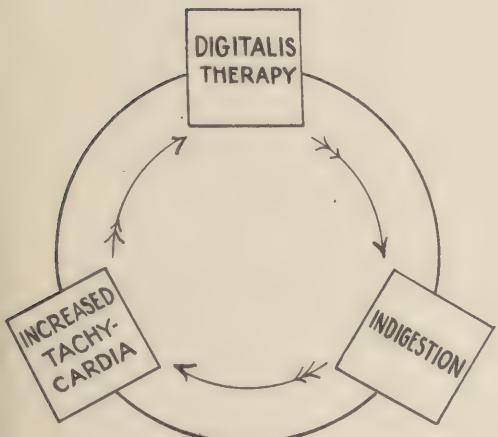
CIRCLE 19 :

In Circle 19 we have, in the abstract, the **internist's conception** of the vicious circle constituting Graves' disease. This has already been discussed in the chapter on Pathogenesis (neuro-endocrine theory).

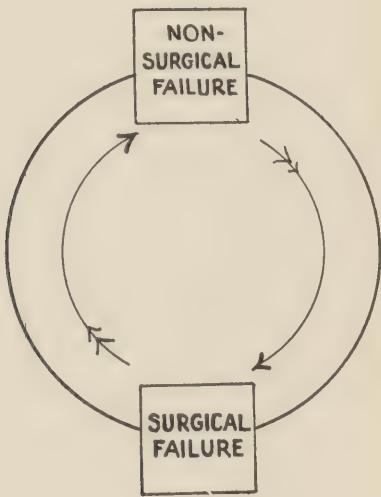
CIRCLE 20 :

The therapeutic Circle 20 consists of a benevolent triad which, properly directed, is capable of neutralizing and effacing the vicious circle constituting the syndrome of Graves' disease. **Psychotherapy**, by producing a state of proper mental receptivity, assists the patient to take the prescribed **rest** and **diet**; mental and nutritional effects being satisfactory, such other measures as **drugs**, **electricity** and the like are productive of good results, and in turn accentuate the results of psychotherapy and diet.

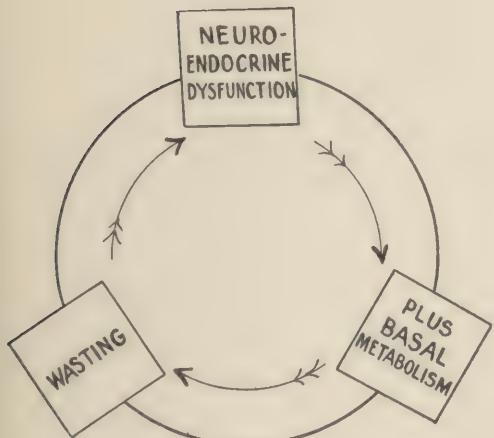
In the presence of satisfactory coöperation, a therapeutic triad of this sort applied by the student of Graves' disease is capable of effecting recovery in all patients who are still sane and who still possess reasonable recuperative powers. These subjects are restored to health and usefulness, and in the course of events even the former predisposition to the syndrome is reduced or eradicated.



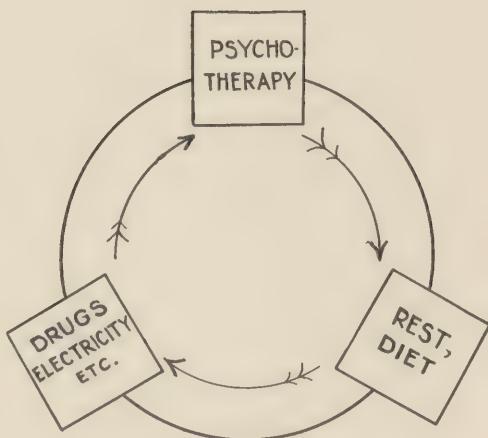
CIRCLE 17.



CIRCLE 18.



CIRCLE 19.



CIRCLE 20.

CHAPTER XVIII

PROGNOSIS OF EXOPHTHALMIC GOITER

No matter how mild the syndrome of the disease has been, there is, theoretically speaking, a certain amount of permanent damage to this or that part of the economy, just as there is a certain amount of scar tissue following a laceration of one of the tissues. Especially is this likely to be true following a severe attack of the disease, in which the various tissues, especially those of the circulatory and nervous systems, have been whipped into excessive function day and night for many months and often for years. It would seem, then, that the word *cure* is not an absolute but a relative term which does not take into account the actual histological status of the bodily structures, but rather the recovery of the *individual* to subjective health, happiness, and usefulness to self and society. However, despite the theoretical implication of a degree of permanent histological damage in these recovered cases, there is evidence to prove that the average patient discharged from a régime of carefully planned nonsurgical treatment begins to enjoy unprecedented health, and his life expectancy is greater than it was prior to the onset of the disease.

Mortality of Graves' Disease.—The death rate of Graves' disease is extremely difficult to ascertain, as it entails a consideration of circumstances beyond the reach of individual observation. Improper diagnosis, the occurrence of fatal intercurrent conditions and sequelæ, the varying mortality rate in the different surgical clinics,—these and many more reasons render our information but of abstract nature. Among the various reports is that of Hector Mackenzie, who states that during the 4 years, 1911-1914, the number of deaths returned in England and Wales as resulting from exophthalmic goiter was 1558 for females and 155 for males, a proportion of 10 females to 1 male. The number of deaths increases in each five-year-age period up to 35-40. In 3 of the fatal cases the duration of the disease was less than six months; in 10 less than one year; in 12 less than two years; in 8 less than six years; and in 6 over six years. In more than half of the cases it was less than eighteen months.

McCarrison claims that in a large number of cases collected for statistical purposes "death occurred in 11.8 percent. of cases from Graves' disease itself, death usually occurring from six months to six years after the onset of the malady; in over 50 perc. of cases

it occurred within 18 months." Blackford reports autopsy of 74 cases, in which 50 percent. of deaths occurred during the ninth month of the disease, and the remainder after the twelfth year. It is evident that the first 12 months of the disease is the period of greatest peril; here are included deaths due to acute Graves' disease, complicating infections, and the first crisis during the course of the average case. Deaths occurring several years later are due not to Graves' disease directly, but to heart failure and other degenerative processes. Dunhill has well said that death is not the only tragedy in Graves' disease. Jessop has collected 25 cases in which an eye had been lost, due to ulceration because of extreme exophthalmos. I, too, have seen several such instances. Other unfortunate sequences regarded by many as worse than death is a water-logged condition of varying duration, with its entailed suffering, a chronic resistant psychosis in which the patient is a burden to self and society, and other conceivable circumstances.

Age and Sex.—In common with diabetes mellitus and phthisis, the younger the sufferer with Graves' disease, the more severe the syndrome, but the prognosis is not graver in the same degree. In the male, the course of Graves' disease is apt to assume a more rapid and severe character than in the female. Not only is this due to inherent reasons little understood, but also to certain psychological attributes such as bad habits, resistance to orders in treatment, and worriment over the care of his dependents, all of which impede favorable progress. In males especially, myocardial degeneration is more apt to become a serious problem.

The Previous Condition of Health of the Patient would affect the prognosis in a given case, because of lack of recuperative powers, and in instances of previous emaciation, because the patient cannot afford to undergo the losses incident to the excessive catabolism of Graves' disease. Thus the prognosis in a frail, nervous, anaemic woman is not quite as good as in one whose weight was excessive and whose general health was relatively good prior to the onset of the disease.

Post-Operative Incidents, such as exhaustion, "acute hyperthyroidism," tetany, hemorrhage, infection and other conditions occurring in clinics in which thyroidectomy is the treatment of choice, add from 3 to 50 percent. to the mortality of certain groups of patients, depending upon the skill used in the selection of cases, the expertness of the surgeon, and the equipment of the hospital. In this category must be included the deaths due to myxedema, insanity, increased susceptibility to infection, and chronic invalidism, which may be regarded as remote postoperative deaths. I have seen quite a few instances of death occurring several hours after ligation. One of these was a young girl of 18 whose parents were urged by a prominent surgeon to yield to surgery as the most sensible means of cure. After a two weeks' presurgical rest cure, during which considerable improvement was

evident, ligation of one superior thyroid was performed at 4 p.m. on a given day; acute delirium and hyperpyrexia followed, and at midnight she died of exhaustion.

The Severity and Duration of the Graves' Syndrome would materially influence prognosis. The prognosis in a patient with a mild syndrome appearing as a persistence of *forme fruste* is good, and appropriate treatment leads to prompt recovery. In many instances in which no treatment is instituted, the patient in course of time may either develop a more serious form of the disease or rarely spontaneous recovery. The acute form of Graves' disease is usually fatal within a few weeks. In the usual chronic form of the disease the mortality rate depends upon the various factors herein mentioned. Generally speaking, in a patient having suffered from the disease during a period of 12 to 18 months, a rational régime of treatment should succeed in effecting recovery within a year. A case of 3 or 4 years' duration may require 14 to 20 months of careful observation ere the patient can be regarded as entirely well. Patients having suffered from Graves' disease for from 4 to 12 years or more present problems of a different nature; the primary disease itself may not require as much attention as the cardio-renal and other organs, the structure and function of which have undergone a varying degree of deterioration. But in the majority of instances even these chronic cases are capable of a restoration to health and usefulness.

Diabetes Mellitus, occurring simultaneously with Graves' disease, affects the mortality of the latter very materially, both from the occurrence of acidosis and from infections. It is difficult in some such instances to differentiate between genuine diabetes mellitus and the transitory diminished carbohydrate tolerance common to Graves' disease. Due caution must be taken in such cases, for, although on the one hand, anti-diabetic treatment must be instituted, rendering the prognosis much graver through the restricted diet and greater starvation of the body, on the other hand this procedure is unnecessary, and glycosuria may be practically ignored, the patient may be fed liberally, and the prognosis is much better.

Miscellaneous Complicating Diseases such as nephritis, arteriosclerosis, the infections, and pelvic conditions may lead to a fatal termination in themselves or through an aggravation of Graves' disease. Hirst pointed out that a gynecological operation on a patient suffering with Graves' disease adds 13 percent. to the recognized mortality of the operation. For example, the 3 percent. mortality associated with hysterectomy is increased to 16 percent. in a subject of Graves' disease.

Tuberculosis, either preceding, coincidental with, or subsequent to the onset of Graves' disease, may so further devitalize the patient as to render the prognosis much graver than otherwise. A percentage of

the most rapidly fatal cases of Graves' disease or of phthisis are probably of this sort. However, in instances in which the pulmonary condition is latent or mild, I have seen very satisfactory amelioration and complete arrest of phthisis following a faithfully applied régime of treatment for the Graves' syndrome. Rest of body and mind, forced feeding, medicinal, psychotherapeutic, and other measures are capable of effecting recovery of a combination of Graves' disease and mild phthisis occurring simultaneously in the patient. The prognosis, therefore, though guarded, is not grave in a case of this sort.

Pregnancy may or may not alter the prognosis of Graves' disease. The marked demand made upon the body by the growing fetus must be compensated for by an ever-increasing quantity of ingested and assimilated food, and where this is unsuccessful, we have two lives at stake. Moreover, when these cases do not abort spontaneously through irritability and hyperactivity of the nervous and other functions, there may be an accidental abortion through the administration of drugs, especially ergotin, or after thyroidectomy, if we do not observe due caution. This subject has already been discussed in a previous chapter.

Circulatory Decompensation with anasarca is the most common cause of death from Graves' disease. Presupposing a heart previously normal in structure and function, a syndrome during which the organ is accelerated but to the extent of 80 to 90 cycles per minute may continue on indefinitely without marked damage to the myocardium; but a heart which beats away at 120, 140, or 160 per minute for years is one which will rapidly give out through degeneration of the musculature, with consequent hypertrophic dilatation, relative insufficiency, first of the left side of the heart, then of the right, and finally a fatal loss of compensation. Though I have observed quite a few instances of heart failure with anasarca respond perfectly to non-surgical management with good nursing, these were probably due as much to *relative* cardiac dilatation as to degeneration. Where there is complete circulatory relaxation due to a 10 or 12 years' siege of Graves' disease, in which it can reasonably be assumed that the myocardium has undergone marked degeneration, the prognosis is guarded.

Insanity during the course of Graves' disease is a bad omen, especially if the psychosis is of the wildly agitative type. The patient utilizes all his reserve energy during the periods of mania, and this, plus the complete insomnia and antagonism to efforts at feeding, usually results in death from exhaustion. There are exceptions to this rule, however. Occasionally, a patient of this sort, expected to die any day, will suddenly surprise everyone by a happy turn for the better, and improvement will continue on to complete recovery. An example of this sort is described in the discussion of nervous symptoms.

Hypothyroidism occurring either spontaneously or resulting from

thyroidectomy is a factor to be included in this category. Deficiency of thyroid function may vary from a mild hypothyroidism to the complete clinical picture of cachexia strumipriva. Removal of the entire thyroid usually leads to death within five years. Though the symptomatology may be mitigated for a time by thyroid ootherapy, the patient is unduly susceptible to the infections.

The Condition of the Digestive Tract alters the prognosis of Graves' disease very materially. An important element in the successful management of the disease is successful overfeeding in order that the ravages of the plus basal metabolism be overcome and the loss of weight be overcome. All things being equal, a good digestion and the freedom from nausea, vomiting and diarrhea are the most useful allies in the treatment of these patients and the best index of an excellent prognosis. On the other hand, a rebellious digestion, associated with a meager food intake, nausea, vomiting and diarrhea, reduce the chances of a prompt and favorable course of events. In some instances, a fatal termination is due directly to this cause. However, in nearly every instance, tactful therapeusis is capable of turning the tide to a favorable outcome.

Early diagnosis constitutes the greatest factor influencing a favorable course and prompt recovery. Graves' disease, in its incipiency, is one of the most elusive diseases in the practice of medicine to diagnose, and at the same time one of the most satisfactory to treat, if therapeusis be promptly and expertly applied. The earlier in the disease the proper measures are instituted, the more prompt are the results produced, for the vital organs are not yet sufficiently damaged in structure to affect the patient's welfare in later life, neither are they so habituated to morbid function as to render the restoration of a proper physiologic balance a tedious matter.

The Mode of Treatment Instituted plays a vital rôle in the prognosis of the case at hand. Unfortunately, there still exist contending schools of treatment, each claiming its own method as the best in the management of the disease, to the exclusion of the others. Meantime, while the arguments hold sway, the open-minded general practitioner is at a loss to know what to do, and the patient is often left to chance or fate. (a) Shall he let the patient go on in the hope of spontaneous recovery? Decidedly no, for though some patients recover untreated, these constitute but a small fraction of the vast number of cases, and to "leave it to Nature" is to jeopardize the life of the patient. Nature errs in many ways in the syndrome of Graves' disease, and it is for medical science to select such remedial measures as will successfully harness and direct Nature to serve the patient in the adjustment of the various vicious circles. (b) Shall it be surgery? Patients subjected to thyroidectomy frequently enjoy transient improvement from

the symptoms of *hyperthyroidism*, but still suffer with Graves' disease, and when the thyroid is regenerated, hyperthyroidism in the fullest degree is again manifested. Aside from the considerable mortality rate of surgical interference with the hyperplastic thyroid, patients surviving thyroidectomy are worse off than those whose thyroid has not been tampered with by the knife. This is mentioned in detail in the concluding chapter of this book. To say the least, the prognosis of Graves' disease under surgical management is hardly better than if the patient were left alone to take his chances with spontaneous recovery. (c) Shall it be x-ray treatment? Here we have bloodless surgery, in that the thyroid secretion is curtailed by the destruction of some of the thyroid structure,—without cutting, shock, scar, and many of the disadvantages of surgery. But the *rationale* is still wrong, since to accept destruction of thyroid structure and function is tacitly to accept the hyperthyroidism theory of Graves' disease, and this is not tenable, as amply proved elsewhere in this volume. Hyperthyroidism is a distinct entity, while Graves' disease is another. So that x-ray treatment, though more acceptable than thyroidectomy, is not the treatment of choice. (d) Shall it be medicinal treatment? Yes and no. No, if by medicinal treatment is meant merely the helter skelter administration of drugs with the vague hope of finding something that will act as a specific in treatment, or even the use of quinin hydrobromid with the idea that it is a specific. Such procedures fail and add to confusion and disappointment. Yes, if by medicinal treatment is meant the elimination of discoverable etiological factors, a carefully outlined régime of physical and mental rest, a carefully planned dietary, the administration of drugs to correspond to the individual's needs, a broad, practical psychotherapy, and other measures, for the proper length of time. With the necessary coöperation, the prognosis in such patients is excellent, and the mortality rate *nil*.

In concluding the remarks on the prognosis of Graves' disease, I can only repeat that a reasonably early diagnosis and the institution of a rational therapeusis should render the outcome a happy one. Death from Graves' disease is preventable and is traceable to late diagnosis, inappropriate treatment, or both. Occasionally, lack of coöperation of the patient and household in a carefully planned and promptly instituted therapeutic régime may lead to disaster—but this, too, can usually be averted by psychotherapy. It is the contention between the various schools of treatment and the scarcity of clinicians who understand the disease and its victim that render the treatment of such a patient an almost unmanageable task, when, in truth, the prognosis in the usual instance of Graves' disease should be far better than that of the usual instance of pulmonary tuberculosis, and recovery should be far more conclusive.

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CHAPTER XIX

GUIDING PRINCIPLES IN THE NONSURGICAL MANAGEMENT OF EXOPHTHALMIC GOITER

Definition.—By the nonsurgical management of exophthalmic goiter or Graves' disease is meant the institution of remedial measures that do not require the usual surgical procedures adopted in goiter clinics. Ligation, thyroidectomy, thymectomy, resection of the sympathetic ganglia, and other measures recently or now practiced in surgical clinics on the assumption that the disease has its origin in the thyroid, thymus, or sympathetic ganglia, are here regarded as contra-indicated. By the nonsurgical management of the disease we therefore include prophylactic, dietetic, hygienic, medicinal, electro-therapeutic, psycho-therapeutic, and other measures indicated in the treatment of these patients on the assumption that the syndrome is due to a widespread dysfunction of all the endocrine organs and of the vegetative nervous system, and that the thyroid enlargement is a result, not the cause, of the disease. As a corollary, it is therefore assumed that therapeutic approach, too, must be widespread and not local.

These remarks apply strictly to exophthalmic goiter or Graves' disease, and not to toxic adenoma, otherwise known as hyperthyroidism. I frankly admit the wisdom of thyroidectomy in toxic adenoma, but I do not accept as rational any operative procedures directed toward curtailing the output of the thyroid secretion through operative procedures upon the thyroid in exophthalmic goiter or Graves' disease. Ample reasons for this stand are given in the concluding chapter of this volume.

RÔLE OF THE SURGEON IN GRAVES' DISEASE

Let it not be understood that in Graves' disease surgical procedures are *never* indicated. In many strictly medical conditions, emergencies may arise requiring incidental operative procedures. The surgeon may be required in typhoid fever in the presence of an intestinal perforation. In scarlet fever, a mastoiditis may require urgent surgical interference. In pneumonia, an empyema requires the knife to save the patient's life. These and other conceivable situations in primarily medical conditions require the services of expert surgery to assist the internist in restoring his patient to recovery.

Imperative Surgical Procedures in the Nonsurgical Management of Graves' Disease.—In Graves' disease, too, the need for emergency surgery may arise. The rare conditions in which the thyroid gland may require operative interference are (a) marked pressure symptoms due to the enlarged thyroid, in which the patient's comfort or life is in danger for *mechanical* reasons; (b) malignant changes within the thyroid gland. These emergency conditions, *i.e.*, pressure symptoms and malignant changes, are very rarely seen to occur in the hyperplastic thyroid of Graves' disease, and are a negligible quantity in the consideration of the nonsurgical management of these patients. Exceptionally, the organ gives rise to pressure symptoms not because of its size, but its *location*, being situated retrosternally or in other anomalous positions, under which circumstances surgery is of course indicated for *mechanical* reasons. The most usual indications for surgical interference in the nonsurgical management of Graves' disease are (c) infectious foci situated in various parts of the economy. For instance, infected teeth, tonsils, nasal sinuses, and the like, infections of the gall bladder and intestines, including the appendix, diseases of the female pelvis such as pyosalpinx, uterine neoplasms, and the like, may require surgical attention. Operation upon these latter is performed on the broad principle that the elimination of infectious foci is just as rational a procedure as the correction of diet, social adjustment, and psychic adaptation so frequently found to be necessary in these patients. Such operative procedures do not indicate surgery to be the means of treatment of Graves' disease; the removal of infected teeth, tonsils, appendix, etc., constitute mere incidents in the broad nonsurgical régime of the management of a patient of this sort.

Infectious Foci in the Pathogenesis of Graves' Disease.—Despite the insistence of many observers that focal infections constitute an important etiological factor of Graves' disease, this has not been confirmed by my observation. Though it must be admitted that infectious foci *occasionally* serve as exciting causes of the patient's plight, in the majority of instances they are purely coincidental, bearing no causal relationship to the syndrome. Again, the syndrome of Graves' disease may precede rather than follow an infectious focus. Why cannot a person with Graves' disease develop infected tonsils, teeth, or appendix as well as anyone else? Indeed, this would seem to occur quite often by virtue of the reduced bodily resistance during the course of the Graves' syndrome. Again, why cannot a person possessing diseased tonsils, pyorrhea alveolaris, or a chronically inflamed appendix develop Graves' disease as well as anyone else? And lastly, I have seen several instances of Graves' disease following shortly upon a removal of infected teeth or tonsils, the operative shock having served as the exciting factor in the predisposed individual. However, despite these apparently contradictory phases of the question, we must, on general principles, act

upon the assumption that it is imperative sooner or later to remove all infectious foci in a patient suffering with Graves' disease.

The careful, interested internist, having made a diagnosis of Graves' disease, typical or atypical, has also attempted to ferret out the etiological exciting factors and has discovered various probable causal factors to be responsible for the syndrome in various patients. In this case it is a psychic trauma; in the other, a sudden shock; here the exciting cause is an extremely trying occupation, and in another instance infected tonsils, teeth, appendix, or a fallopian tube seems to be responsible for the instigation of the syndrome. However, the removal of a localized diseased process away from the thyroid having become an element in treatment, too much stress must not be placed upon it as responsible for the *continuance* of the syndrome. Tonsillectomy, for instance, must here be performed on general principles, but not as a curative agent. The tonsils may be compared to a torch, which, having started the conflagration, is no longer a factor in the result. The same may be said of other focal exciting causes of Graves' disease. Their elimination is, of course, necessary, but only as a constituent of an otherwise broadly outlined regimen of nonsurgical measures calculated to overcome the widespread Graves' syndrome.

When Best to Remove Infectious Foci is a very important problem, for upon it may depend the prognosis of the case. To let an infectious focus remain indefinitely or to believe that it may be entirely ignored is unscientific practice of medicine. Infectious foci must be removed sooner or later if we are to expect permanency of good results in treatment. Assuming that we are dealing with an instance of badly diseased tonsils, when is the best time to remove them? I have been guided by two factors, the first of which is the degree of inherent nervous excitability of the patient. In a subject who regards an operative procedure with little or no anticipation or excitement, tonsillectomy may be performed with a minimum of deleterious reaction. Operative recuperation is brief and satisfactory, and the patient continues more rapidly than ever to improve under the nonsurgical management of Graves' disease. On the other hand, a patient who is inherently excitable in nature will give the internist trouble after tonsillectomy, for there may be an extreme flaring up of the syndrome. By inherently excitable, I have reference to the state of nervous reaction following operative procedures, aside from the excitability that comes with the Graves' syndrome. The second factor is the stage of the disease. In general, I should prefer to see a tonsillectomy performed at once, if the patient is suffering with the very early or *forme fruste* stage of the disease. But if the syndrome is well developed, it is usually the best policy to extinguish the conflagration, as it were, prior to tonsillectomy. The disregard of the time element in the performance of tonsillectomy has been the cause of serious consequences in many patients.

During the height of Graves' disease, the slightest added shock, whether it be emotional strain, psychic trauma, or tonsillectomy, may so accentuate the syndrome as to convert an ordinary clinical picture into one resembling acute Graves' disease, with added peril to the patient. I have also observed that even in patients who are *nearly* well but inherently excitable, a tonsillectomy may bring on a complete relapse, causing a return of the original syndrome. To summarize, focal infections and other localized conditions requiring surgical procedure as an incident to a broad nonsurgical management of Graves' disease, should be taken care of immediately if the patient is in the formative stage of the disease and is not exceptionally excitable. But such procedures must be postponed until all evidences of the disease have disappeared if the patient comes under treatment during the frankly outspoken stage of Graves' disease. This latter statement holds good even though the patient pretends a courageous attitude and insists upon immediate removal of the focus.

RÔLE OF THE INTERNIST IN GRAVES' DISEASE

The Physician Himself is the guide of the patient's destiny. Unfortunately, Graves' disease has not been taken seriously enough from a therapeutic viewpoint by the general practitioner. It is admitted that the surgical approach is fraught with a lessened operative mortality rate and neater scars than heretofore, but this is a makeshift and speaks little, if at all, for progress. The great lack has been a relative lack of interest in the study of non-operative remedial measures capable of assisting these unfortunates back to health and happiness. If the profession were to devote half as much attention to Graves' disease as to tuberculosis (and Graves' disease in its various forms is at least 50 per cent as prevalent as phthisis), or, if as much interest were given to nonsurgical as to surgical procedures, the disease would cease to be the burden that it has been, and nonoperative recovery would become the rule. The general practitioner, knowing little about Graves' disease and less about its therapeusis, is only too glad to turn the "case" over to the surgeon, with or without a period of unsuccessful treatment. The "case" is regarded as one of "toxic goiter,"—a lump requiring removal. The utter fallacy of this attitude reflects upon the physician, but still more upon the patient's welfare and life itself.

Graves' disease, to be successfully managed, requires intensive, conscientious study. It is a broad field in itself,—at least as large a field of endeavor as any other specialty in medicine. In no other disease are the inherent foibles and frailties of body and mind brought so clearly into the limelight; in no other morbid condition do we see so sick a mentality in so sick a physique; in no other syndrome is

the entire physical and neuro-endocrine make-up so deranged; in no other malady is the patient so frightfully burned up by the tremendous oxidation of the tissues, and, despite these apparent handicaps, *in no other disease is recovery so assured and restoration to self and society so constant as in Graves' disease if the medical attendant, understanding and speaking the language of his patient, creates an atmosphere of harmonizing coöperation between himself and his charge.*

Individualization in Treatment.—In no other class of patients must discrimination be the guiding factor in therapeusis as in Graves' disease. Individualization in the treatment, it must be emphasized, though guided by findings in the patient, is really a quality of the physician; the patient has little to do with it. It is the physician who must recognize the need for discrimination, and who must select in a discriminating way those remedies which are more apt to effect a speedy improvement in the patient at hand. In every branch of the therapeusis of the disease individualization must be the guiding factor, whether it be hygiene, diet, medication, electricity, psychotherapy, and what not. While one patient may improve by the use of cold baths, another may become nervous, requiring tepid or warm tub baths; while most patients readily respond to a strictly nonflesh dietary, the occasional individual requires the addition of a veal or lamb chop or a small portion of bacon now and then in order that the appetite and digestion, disturbed because of psychical or other factors, be enhanced. While a certain group of patients improve excellently on the inclusion in medication of iodin or its salts, many become worse under its administration. Electricity, mental adjustment, social rectification, vocation, avocation,—all these enter into the question of individualization in treatment. It must be said, however, that in view of the fact that there are a few clinical evidences in common in many patients, certain broad principles in treatment also obtain in these, individualization entering as a modifying factor. Thus, for instance, a nonflesh dietary may be the generalization upon which diet is based; rest of body and mind is another generalization; the administration of quinin is harmless to all these patients, though there are instances in which its administration is useless.

There is no specific method of therapeutic procédure simply because there is no specific etiology or symptomatology characterizing the affection. Indeed, the chief characteristic of Graves' disease is its variability. All cases differ markedly, and though the four cardinal symptoms command our respect, they must not as a group be taken too seriously in a given patient. Thus we note an absence of exophthalmos and of goiter; we may note a varying combination of hyperthyroidism and hypothyroidism, a combination of sympatheticotonia and vagotonia; in one patient there may be emphatic evidences of adrenal, in another gonadal, in still another pituitary, and again pan-

creatic or parathyroid involvement. In one patient, the heart is still in good condition; in another the organ is badly degenerated with evidences of circulatory decompensation. One patient is still tolerably sane and sensible; another wavers, is obsessed with fixed ideas, or suffers from hallucinations and delusions, is a nymphomaniac, or is about to merge into a major psychosis. We might continue for hours to enumerate variations in the clinical picture of Graves' disease, bearing more or less on the nature of treatment to be adopted in an individual case. Any treatment, to succeed, must coincide with the probable individual etiology, individual symptoms, and individual peculiarities and idiosyncrasies. Hence it is that the management of such a patient is one of the most difficult, if not the most difficult task in medicine. Hence it is that such a patient is often a burden to the general practitioner and a source of worriment to the surgeon.

The armamentarium of the physician must be ample enough to enable him to discover a set of remedies applicable to the case in question, which remedies will act in a more or less specific fashion in the patient in accordance with individual indications. He must endeavor to eliminate through therapeutic agility the causal factors, break up causal relationships and vicious circles, overcome the most distressing symptoms, and thus actually effect recovery from the syndrome. The overcoming of symptoms is indeed an important matter and must always be borne in mind as a constituent of a rational therapeusis of Graves' disease, as indeed of any disease in the practice of medicine. This is not merely symptomatic or empirical, but really rational treatment. Such symptoms as indigestion, diarrhea, palpitation, restlessness, insomnia, and many others, if not alleviated by so-called symptomatic remedies, will render futile all other more basic therapeutic measures. Hence, individualization in the selection of remedies must not only embrace measures to overcome the basic factors of the disease itself, but also the various subjective signs and symptoms.

The physician's skill, however, though the guiding factor, must be supplemented by the coöperative attitude of the patient.

COÖPERATION OF THE PATIENT IN TREATMENT

The first essential in the outlining of a régime of treatment for the patient is the inculcation into his mind that orders must be strictly obeyed. The medical attendant may find it useful to address his patient in this manner: "From now on until you are discharged cured, you are on a ship and I am the captain, guiding the ship and your destiny. You are a mere passenger incapable of directing your future during the period of time constituting the voyage. The ship is steered in just the way that I, the captain, see fit. You, the passenger, are bound for the haven of safety and happiness, if you do not interfere

with the captain's instructions." Aside from information which the patient may offer to the doctor regarding the history and symptomatology and the subjective result, beneficial or otherwise, of remedial measures instituted, the patient must have nothing to say concerning the management of the case, but must obey implicitly every detail of treatment. *Military discipline*, in letter and in spirit, should characterize obedience to instructions. The patient who promises to do everything and does little will not get well, will discredit his physician, and destroy himself. The details of treatment must not be left to the memory of the patient. Everything must be put in writing at the very start, and the patient must be informed kindly but firmly that unless a strict, faithful, religious obedience to instructions obtains, it is useless to begin treatment at all. The physician must not be satisfied with a mere "I'll try" or "I'll do my best." The patient must be made to state enthusiastically "*I shall obey all your orders!*" at the first visit. The patient must be imbued with *his* importance as a vital factor in his recovery. He must be made to understand that no matter how expert the treatment, it is useless unless orders are unequivocally obeyed. There must be no element of weakness manifested during this moment of trial. The promise to coöperate must come from the very heart of the patient, and his words, stated in this positive fashion, must imbue him with the sense of impending recovery. Far from feeling offended at the doctor's attitude in forcing the promise from him, the patient will respect him and feel that finally he has placed himself in the hands of a master who understands the disease and its treatment. It is this attitude, and no other, begun at the very start and continued on throughout the period of treatment, that spells success.

Conditions Modifying Discipline.—Under certain circumstances, however, the discipline of treatment cannot be carried out ideally. The chief reason is usually insufficient funds. In addition to the need of some one to take care of the household and perhaps to wait upon the patient, the ample diet required and the druggist's bills are added items of expense. Frequently, a young married woman with a child or two, is left at home with no assistance, the husband, of necessity, having to absent himself the entire day to earn the livelihood. Thus it is that the patient must answer the frequent summons to the front door, prepare the meals, take care of the children and of herself. Perhaps this very overwork played an important etiological part in her condition. This is a sad situation of affairs, for favorable progress under these circumstances appears almost impossible. A patient of this sort must therefore be managed as much from the sociological viewpoint as from other angles, and it is necessary for the physician to acquaint the other, perhaps more distant relatives, of the existing plight. Some one must come to the rescue, and some one usually does.

Co-operation When Improved.—An attitude of waning sincerity and

enthusiasm must be anticipated early. At the very start, the patient must be informed of the probable duration of active treatment and of the unreliability of the subjective sense of well-being as an index of complete recovery. Forewarning the patient and his family in this manner will, in most instances, safeguard the future. However, despite the doctor's foresight and warning, some patients forget. The slightest tendency toward irregularity in visits to the doctor's office must be construed as the first step toward sudden cessation of coöperation or of treatment, and the necessary warnings must be issued that unless the enthusiasm as originally evinced be maintained during the entire period of necessary treatment, all previous effort and benefit will be lost. Under such circumstances, I tell my patients to regard each week as the very first week of treatment, so that the earnestness and morale in coöperation be continued until recovery is secured and the patient discharged.

One of the most serious difficulties with patients who have already improved under treatment is their error in regarding improvement as recovery. Having been an invalid for months or years and finding himself in possession of a surprising sense of well-being, the patient construes this improvement to be a state of actual cure. On the assumption that the doctor is overly careful, or "particular," or mercenary, and that he is desirous of continuing medical attention indefinitely, the patient either discontinues treatment or becomes irregular and infrequent in visits and slipshod in obedience to instructions. At any event the charm of military discipline to instructions is broken; the patient has freed himself of what is now termed the thraldom of the doctor's sway, and has once more become independent and free to follow personal likes, dislikes, and inclinations.

For instance, a woman of 30, in desperate condition at the first consultation because of a badly damaged heart, appeared to improve satisfactorily during the first few weeks of treatment, when I suddenly discovered that her condition was becoming as bad as it was at first. On inquiring into matters of coöperation and obedience to orders, she confessed that she had not been obeying instructions at all. She had assisted in moving her household into another residence and after having completed this task proceeded like a good housewife to haul one pailful of water after another up and down the stairs for scrubbing purposes. During one of these trips with a bucketful of water, she tripped and fell down a half flight of stairs. As a result, the patient now appeared in such condition that it was necessary to place her at complete rest in bed for three months. This was accomplished with the assistance of a now coöperative household, the members of which carried out most faithfully their promise to coöperate in treatment.

Another patient, a woman of 28, suffering with Graves' disease of severe type, improved very satisfactorily under treatment until the

fourth month of therapeutic effort was reached, when further progress seemed very difficult to obtain. On my inquiries regarding coöperation she disclaimed any infraction of orders. I was puzzled over this patient when my assistant informed me that during a short conversation with her she confessed disobedience to almost every order except the taking of medicines. Here was a case of very apparent deception by the patient. When I spoke to her about this, she admitted that she was deceiving herself even more than she was deceiving me, and realizing the harm that she was doing herself, promised from then on to coöperate religiously with efforts in her behalf. This was actually accomplished with the assistance of a heart-to-heart talk tinted with considerable sternness, in which an appeal was made to her instinct of self-preservation. Favorable progress was uninterrupted from then on.

Abrupt Discontinuance of Treatment.—In a percentage of patients it is impossible for the internist to have the pleasure of formally discharging the patient. Rarely this is due to circumstances over which the patient has no control, as, for example, environmental conditions. Usually the cause is the fractiousness of the patient. Having been markedly improved through a few months of treatment, and desirous of again resuming old habits, the patient simply discontinues treatment abruptly and the doctor sees no more of him. The following case histories will illustrate this very important situation:

CASE 1, a widow, age 44, was referred for treatment October 14, 1921.

Chief Complaints: Goiter, weakness, insomnia, nervousness, shortness in breath, palpitation, dysphagia, occasional diarrhea. Duration of illness 10 years.

Family History: Her mother died of uremia at 72. Her father is living and well at 75. Otherwise the family history is negative.

Previous Medical History: She had measles and whooping cough as a child, and typhoid fever at 21.

Social and Personal History: Menstruation began at 14 and had always been regular. She married at 23, and had one child 18 years ago, and one miscarriage of 5 months' gestation without untoward results. Her husband died 6 years ago, since which time she has been obliged to earn her livelihood. She takes tea, coffee, and meats moderately. The patient claims to have been of a congenial temperament all her life until 10 years ago, when her present illness began.

Present Illness: Began 10 years ago when she noticed a slight fullness of the neck. Though this did not seem to give rise to constitutional symptoms, it continued to grow slowly and persistently. Following the death of her husband 6 years ago, the patient, overwhelmed with grief, became extremely nervous, suffered with restless sleep, palpitation, and an increase in the size of her goiter. Four years ago, when her mother died and shortly afterwards when her sister died, there was a further accentuation of all her symptoms to which were added extreme palpitation, progressive loss in weight, diarrhea, further enlargement of the size of the neck, and marked weakness. These symptoms continued progressively until the present time. Her weight, which 6 years before was 168 pounds, is now 95½ pounds.

During the past few years she has been noticing bulging of the eyes, and occasionally swelling of the ankles.

Physical Examination: The patient is a very frail, dark complexioned white woman, resembling in facies somewhat the appearance of an Egyptian mummy, in that her drawn features are discolored to an almost bronze tint by evident suprarenal involvement. She is 5 ft. 5½ inches in height, weighing 95½ pounds, and is so weak that she is obliged to sit down upon the first chair she can reach. The skin is almost uniformly bronzed, wrinkled, and is thin and moist to the touch; dermographia is easily elicited. The teeth are in very poor condition, but are at present under repair. The tonsils are moderately inflamed. The eyes are moderately exophthalmic, and the tissues about the eye balls are edematous; all the characteristic eye signs of Graves' disease are present. The thyroid is unusually large for a case of



FIG. 82.—Patient described in case 1. Exophthalmic goiter of 10 years' duration. Pulse rate 140; heart action tumultuous and merging into auricular fibrillation; weight 95½ pounds.



FIG. 83.—Same patient after 6 months of treatment. Pulse rate is 72; heart action entirely normal and rhythmical; there is gain of 31½ pounds in weight. At this point the patient discontinued treatment abruptly.

Graves' disease—the goiter is diffusely distributed, corresponding accurately to the horseshoe shape of the normal thyroid. Palpation reveals no thrill; the mass is resistant to the touch and noncompressible. On auscultation a distant bruit is scarcely audible. In general the physical examination of the thyroid indicates a combination within the mass of an admixture of adenomatous and hyperplastic pathology. The heart is enlarged to the left anterior axillary line and presents the physical signs of moderately advanced myocardial degeneration. The heart rate is 140, is exceedingly irregular and appears to be merging on a state of auricular fibrillation. The lungs present no tangible disease. The abdomen and limbs are practically negative. The reflexes are heightened. Tremor is universally distributed and is coarser than is commonly observed in Graves' disease.

Psychic Condition: There is the quickeening and slurring of speech frequently observed in these patients; the voice is hoarse and otherwise altered

through persistent compression of the goiter upon the larynx; there is a quickening of ideation and of muscular movements, resembling in many respects a mild form of chorea. Despite the extreme weakness and precordial distress, the patient still claims to be feeling good, and asks when she can resume work. Altogether, however, there are no distinct evidences of irrationality, and the patient seems to be willing to coöperate faithfully with instructions in treatment.

Laboratory Data: Basal metabolism is plus 60; quinin test is positive, sugar tolerance considerably reduced.

Diagnosis: Chronic progressive Graves' disease of several years' duration with adenomatous changes in the hyperplastic thyroid.

Course Under Treatment: Coöperation of the patient was at first entirely satisfactory and within 6 months the patient gained 3½ pounds, with an associated diminution in size of the goiter and in eye symptoms, a restoration of heart frequency and rhythm to normal, and a complete sense of well being, so that she repeatedly expressed herself as "feeling fine" and was desirous of knowing when she could resume working. At this point, her father to whom the house where she was residing belonged, sold the property, and the patient was obliged to seek quarters elsewhere. This so upset her that she discontinued treatment.

Summary: A patient with Graves' disease of progressive type and of several years' duration, with myocardial degeneration and Addisonian symptoms, had gained 3½ pounds in weight, complete subjective health, marked improvement in the thyroid and in eye symptoms, and was progressing rapidly toward recovery after 6 months of active treatment, when she discontinued treatment abruptly because of a sudden environmental emergency.

CASE 2. a business man, age 40, was referred by Dr. H. N. Diamond, of Philadelphia.

Chief Complaints: Diarrhea, nervousness, insomnia, loss in weight, weakness in lower limbs, sweating. Duration of illness 16 months.

Family History: The patient's mother is nervous, otherwise the family history is negative.

Previous Medical History: The patient claims never to have been sick prior to his present illness.

Social and Personal History: He was married 18 years ago and has 5 children living and well. He claims that his home environments are congenial. He partakes moderately of meats and tobacco.

Present Illness: Seventeen months ago, while driving an automobile, his car collided with a motorcycle. A month later, he felt himself becoming exceedingly nervous, which led to a "nervous breakdown." Shortly thereafter, there gradually developed enlargement of the neck, bulging of the eyes, palpitation, trembling sensations all over the body, and paroxysms of diarrhea with 10 or more movements a day. Insomnia became troublesome, and the weakness in his limbs became so severe as to make it impossible to attend to his daily duties. There has been a considerable loss in weight. Twelve weeks ago, the patient underwent a double ligation, but there was no alleviation of his symptoms from the operation.

Physical Examination: The patient is a white male adult, 5 feet 6 inches in height, weighing 117 pounds. The skin is soft and moist, presenting moderate dermographia. The teeth are in good condition, the tonsils are moderately inflamed, and there is the appearance of typical smokers' sore throat. The eyes are moderately exophthalmic, presenting all the character-

istic signs of Graves' disease. The *thyroid* is markedly hyperplastic, the swelling being symmetrically distributed. The greatest circumference of the neck is 15½ inches. There is a scar of the aforementioned ligation to be seen on each side. On palpation the thrill is felt, and on auscultation the mass reveals a double bruit synchronous with the cardiac cycles. The heart is slightly enlarged, extending to just outside the midclavicular line to the left. The heart sounds are more violent than normal, and the rate is 110 per minute. The *lungs*, *abdomen* and *limbs* are negative. The *reflexes* are exaggerated. The typical *tremor* of the outstretched fingers and toes is present. There is also a trembling of the entire frame, as evidenced by the vibratory sensation transmitted to the examiner's hand when placed upon the patient's shoulder.



FIG. 84.—Patient described in case 2. He had undergone a double ligation following which the syndrome became aggravated. Weight was 117 pounds; heart rate 110 per minute.



FIG. 85.—Same patient as in Fig. 84 after 3 months of treatment. There is a gain of 24½ pounds in weight and a reduction of the pulse rate to 80. At this point the patient discontinued treatment abruptly because he was unwilling to coöperate with instructions.

Psychic Condition: The patient states that he wants to get well, but that to stop tobacco is unreasonable and to rest in bed 16 hours a day for a few weeks is inconsistent with satisfactory progress in his business. When I informed him that all my orders are final and must be obeyed, he reluctantly promised to coöperate. It could be seen, however, that he would soon become fractious and unreasonable.

Diagnosis: Graves' disease tending toward a crisis, as evidenced by the patient's initial attitude toward treatment.

Course Under Treatment: As the patient's home was in a distant town, it was not possible to have him call more often than once a month. At the termination of 4 weeks of treatment the patient's weight was increased by 9 pounds, and there was very evident general improvement. However, sensing a tendency toward disobedience to instructions, I warned him that unless

coöperation would be unequivocal, I would refuse further attention. The next 8 weeks saw a complete transformation in the patient. There was a total gain of 24½ pounds in weight, the heart rate was 80 per minute, the eyes were very much improved and there was such a satisfactory sense of well being that the patient begged to be permitted to return to his business. One month later he returned for another observation. At this time, close observation revealed the fact that there was a return to tobacco. On questioning him, he confessed to taking "3 or 4 cigars a day." (I really believe he took double that number.) I again warned him that unless promises were kept, I would absolutely refuse further attention. He promised to begin all over again and obey instructions. This was November 24, 1922, and I have not seen him since.

Summary: A man of 40 with Graves' disease of 16 months' duration and who had undergone a double ligation without improvement, progressed most satisfactorily during 3 months of nonsurgical management with a gain of 24½ pounds in weight, a reduction of the pulse rate to 80, and marked subjective and objective improvement, discontinued treatment abruptly because it was insisted upon that he must abstain from tobacco.

CASE 3, a manufacturer, age 59, referred February 7, 1922.

Chief Complaints: Nervousness, insomnia, palpitation, loss of 50 pounds in weight during the past 2 years, weakness of the legs. Duration of illness 2½ years.

Family History: His father was afflicted with palpitation, and died of alcoholism; his mother died of apoplexy; a sister has bronchial asthma; a daughter died of tuberculosis 1½ years ago. The patient ventures to say that the entire family is more or less nervous.

Previous Medical History: He had measles as a child; influenza in 1921.

Social and Personal History: The patient was married 39 years ago, had 7 children, 5 of whom are living. He does not eat meat and takes 2 cups of coffee daily. He smokes and chews tobacco excessively. He seems to have been of rather irritable temperament, quarreling with relatives and friends on the slightest provocation.

Present Illness began 2½ years ago, following what the patient terms a "business shock." There was an onset of extreme nervousness, palpitation, restless sleep, anorexia, nausea, and paroxysms of diarrhea. It was soon noticed that there was a very marked loss in weight and strength; the neck became somewhat full in front, and the eyes became prominent. These symptoms became progressively worse up to the present time.

Physical Examination: The patient is a frail, nervous, irritable-looking man, 5 feet 7 inches in height, weighing 117½ pounds. The skin is moderately moist; there is moderate dermographia. The teeth are in poor condition. The tonsils and entire throat are chronically inflamed, probably due to the persistent irritation from tobacco. The eyes are moderately exophthalmic, with rather severe chronic conjunctivitis; all the other eye signs characteristic of Graves' disease are present. The thyroid is slightly enlarged on inspection, moderately hyperplastic on palpation, and on auscultation there is the typical bruit. The heart on physical examination presents all the signs of progressive myocardial degeneration; the left border extends to the anterior axillary line and downward into the seventh interspace. The heart sounds are uncertain and irregular; there is auricular fibrillation. The pulse rate is 104. The lungs and abdomen are negative. The reflexes are exaggerated. Tremor is coarser than usual and involves the entire voluntary muscular system.

Psychic Condition: The patient is hasty and irritable, almost to the point of arrogance. Mentality is hyperacute, but misdirected into channels which render his presence more or less unwelcome to those about him, though he cannot be said to be irrational. His conversation seems to prove that his god has ever been the dollar mark, as he boasts about his business exploits and his frequent trips to Europe. It was necessary to employ a bit of psychotherapy at once, in order to put him into the proper mood for the necessary examination.



FIG. 86.—Patient described in case 3. Severe type of exophthalmic goiter with myocardial degeneration and auricular fibrillation. Pulse rate 104 pulse deficit approximately 100; weight 117½ pounds.



FIG. 87.—Same patient as in Fig. 86 after 3 months' treatment. Eyes nearly normal; heart regular and rhythmical; pulse rate 80; there is a gain of 24½ pounds in weight. At this point the patient abruptly discontinued treatment because we did not agree on the tobacco question.

Laboratory Data: Basal metabolism was not performed, because of the psychic attitude of the patient; quinin test was positive; sugar tolerance was slightly below normal.

Diagnosis: Graves' disease of progressive nature, with marked myocardial degeneration.

Course Under Treatment: The most difficult thing was the matter of cessation of the use of tobacco. "I have been chewing tobacco for more than 40 years and to deprive me of this pleasure is to take away the pleasure of life itself." This was his argument, which I could only meet by an appeal to his instinct of self-preservation. He was informed that his heart would never improve, but would be the cause of his death, if he continued the use of tobacco. This seemed to put him in the necessary mood, and he promised never to touch tobacco again. Six weeks after the institution of treatment, the patient had gained 15 pounds in weight, auricular fibrillation gave way

to a very regular heart action with a rate of 80, and the patient expressed himself as feeling "wonderful." Indeed, from an irritable, gloomy, fractious patient, he was transformed into one capable of smiling and of seeing two sides of an argument. He kept repeatedly asking when he could return to his business, as his presence was demanded there. At the termination of the third month of treatment, the patient weighed 142 pounds, a gain of 24½ pounds; his heart was subjectively normal, objectively remarkably improved, its action being regular, rhythmical, and its rate normal. The thyroid gland was scarcely palpable, and his eyes almost normal. At this point, the patient again rebelled on the tobacco question, for a week later, I noticed a beginning of heart irregularity and also a tiny bit of chewing tobacco on his lip. On inquiring of him how much tobacco he was taking, he confessed to breaking his promise, but stated that he would take no more thereafter. Subsequent visits indicated that he was not only chewing tobacco in as great a quantity as ever before, but that nearly all the other instructions in treatment were being ignored. After several warnings that coöperation was the only condition upon which I would continue treatment, he finally seemed to have decided that the consumption of great quantities of tobacco was far preferable to a restoration of health, and discontinued his visits at just about the time when I had made up my mind to inform him that further treatment under these conditions was futile.

Once in a while a patient having obtained a certain degree of improvement may suddenly drop out of sight, and at some future time, six months or a year later, may call on the physician a well person. The patient shakes hands heartily with the doctor who at first sight may or may not recognize him as a former patient. "Why, what became of you?" the doctor may say. "You are certainly looking fine!" "Doctor," the patient may respond, "I came back to thank you for what you've done for me; I felt so well after three or four months of your treatment that I decided not to ask you about going back to work. I went back to my old job, kept on taking the medicines and your diet, and have been feeling fine; my eyes and neck are entirely normal, and I never weighed so much in my life!" While this is an exception to the rule, it may occur in a small percentage of cases. It so happens that this percentage requires but the impetus of psychical encouragement, successful medication, diet, and rest for a brief period of time, all of which constitute, as it were, a good start. Nature does the rest. Whether spontaneous recovery would have occurred in an instance of this sort, it is difficult and perhaps risky to assume. The fact remains that the first few vital steps in the correction of the morbid process having been attained with the aid of the medical attendant, the goal is reached without further assistance.

COÖPERATION OF THE HOUSEHOLD AND OTHERS IN TREATMENT

The spirit of coöperation in treatment must pervade the entire household as well as the patient. Wife, husband, brothers, sisters, relatives,—all must feel it their duty so to comport themselves as to make for

a maximum amount of benefit to the patient. The helpmate, let us say the husband, for instance, may not understand the gravity of the situation and may so belittle the necessity of strict obedience of orders as unconsciously to interfere with progress. If this be discovered by the physician, it is well to have a personal conference with the husband, so that the nature of the disease can be explained in simple but certain terms, and the necessity for continuous, prolonged coöperation be emphasized. Thus a probable unfavorable atmosphere is converted into a favorable one, and the apparent interested attitude by the physician is usually productive of success in a case of this sort. To illustrate, the wife of a young pedagogue was placed under my care for the treatment of typical Graves' disease of a year's duration. It was discovered that the proper rest, modification of diet, and other instructions were not carried out during the first few weeks. I warned my patient that unless instructions were obeyed, I would not continue treatment. In response, she began to weep and confessed that she was willing and anxious to coöperate, but her husband could not understand her nor the necessity for being so strict. I had him call for an interview and during the prolonged conversation which followed it was evident that he was a neurasthenic, very impatient, and could not possibly see why he should indulge his wife's "petty whims." Moreover, he insisted that he was more sick than she. It was a difficult task, but I finally succeeded in bringing about a mental adjustment in *him* to the extent that he permitted his wife to stay with her parents until she was discharged cured, following which event the couple were reunited and "are living happily ever after." Again, a girl of thirteen suffering with typical Graves' disease was progressing very satisfactorily under treatment for ten weeks, following which matters began to retrogress. On inquiry, the child sobbingly told me that her big sister teased and jeered her and called her names because she was not up and about with the rest of the family. It required a bit of diplomacy, tact, and perhaps a knowledge of the psychology of the adolescent to finally succeed in affecting an adjustment in the atmosphere of this household. This accomplished, improvement again became continuous, and the patient made a satisfactory recovery.

Influence of Friends and Distant Relatives.—Individuals outside of immediate relatives may through their influence assist or impede progress. In this category must be included "friendly" neighbors. These persons frequently inject ideas into the patient's mind which interfere with the necessary mental poise. Inquiring friends, neighbors, and distant relatives too often possess a morbid curiosity regarding the patient's condition, recall the death of this one or that one under similar circumstances, and entice the patient to enter into the conversation to talk about her condition. All this serves as a psychic trauma, interferes with progress, and invites relapse. It is preferable to forbid

such persons from visiting the patient. The household should be made as cheerful as possible; it must be quiet and present an evident atmosphere of harmony and tranquillity. All persons concerned in the patient's welfare must be apprised of the fact that an ordinarily unimportant shock, excitement, mental strain, or the like may bring about an outburst of emotion distinctly inimical to progress. For instance, in a recent patient who was nearly well, the sudden news through the agency of a friendly neighbor that someone a few doors away had suddenly died, was responsible for an exacerbation which required several weeks of intensive therapeutic effort to overcome. An atmosphere which excites, irritates, or perpetuates constant tension and strain is one in which the patient will not progress favorably; a household in which all is sunshine and song will make for peace and harmony within the patient, and prompt recovery will follow.

There are individuals, not necessarily relatives, friends or neighbors, whose influence could bear directly or indirectly upon the progress of the patient. In an individual affianced, for example, problems may arise which must be taken seriously into account. Certain phases of this problem are discussed elsewhere in this book. The frequency, hours, and manner of meeting, the attitude of the one toward the other, and the attitude of the parents of both persons concerned may mean discord or harmony within the patient's mental make-up. The reader can probably imagine many instances of negative or positive situations in this regard.

In an individual who was employed up to the time of the institution of treatment, the attitude of the employer plays its part in the sense of tranquillity possessed by the patient. An employer who is indifferent to the sufferings and financial stress of the patient may be responsible for impeding the favorable course of the therapeutic events. On the other hand, the reverse is the case if the employer is considerate and kind. For instance, in a recent patient who was required to abstain from work for eight months, progress was smooth and satisfactory largely because her employer paid her a satisfactory compensation during her period of disability. When she was discharged cured, she returned to work, and is at this writing happier than ever.

Even the minister plays his part, and at times an important rôle, in assisting the patient to recovery. For example, in a recent female patient of 38, whose mental status was amounting to a major psychosis, it was impossible so to adjust her attitude as to make her take the necessary food, medication, and rest. Her rapid downhill progress was arrested after I had several conferences with her minister, during which I explained what I thought to be the necessary psychotherapeutic tactics which he and I were to employ. Since the patient's mental aberration consisted largely of unwarranted scruples and delusions of a religious

nature, the minister's assistance was of inestimable value, and in course of time the patient made a perfect recovery.

IMPORTANCE OF EARLY TREATMENT

The time of the institution of treatment of Graves' disease is a vital factor, as upon this may depend not only the future usefulness of the patient, but life itself. Unfortunately, the syndrome is not frequently diagnosed in its early stage, and the patient may be compelled to go the rounds from doctor to doctor, clinic to clinic, receiving attention for almost any ailment but that for which he should be treated. Many of these patients, discouraged because of repeated failures of the medical profession, resort to quack medicines, osteopathy, chiropractic, Christian Science, and various other cults. The result is that the condition progresses from bad to worse, partial disability becomes total disability, and the patient, now presenting large neck and bulging eyes, is finally recognized as a subject of exophthalmic goiter. Conditions are frequently even worse, for in the great number of instances in which exophthalmos and goiter are lacking, the affection may remain undiagnosed until the heart has become irreparably damaged. I am frequently told by patients that during the first year or two of subjective complaints, the diagnosis was variously dubbed as early consumption, nervous indigestion, nervous heart, neurasthenia, ulcer of the stomach, and other conceivable conditions. These patients had all been previously prescribed for, some having undergone gastric lavage; in an occasional instance an exploratory operation was performed in efforts to overcome a supposed gastric or biliary condition.

Early diagnosis and early institution of treatment are not the only conditions favoring the patient's prompt recovery. The really necessary factor is *early proper* treatment. Assuming in a given case that the diagnosis was correctly made during the early stage of the disease, the general practitioner has again a difficult problem to face, namely, the differences of opinion among the medical profession as to what had best be done for the patient. This question, especially the matter of surgical versus nonsurgical treatment of Graves' disease, is discussed elsewhere. We must say this, however, in amplification. Unless the *proper* kind of treatment is instituted in the *proper* manner, by the *properly* equipped internist, for the *proper* length of time, the results will be identical with those following belated diagnosis or repeated thyroidectomies. The patient will not emerge from the syndrome safe and sound, but will continue onward in a state of invalidism with finally a badly damaged heart and decompensation, or the end may be due to some other intercurrent condition. The patient's life expectancy, future welfare and usefulness to self and society depends upon the prompt institution of the *necessary* treatment, which is tantamount to saying

that *the fate of the subject depends not upon the disease, but upon the physician in charge.* In this relation both patient and doctor must thoroughly understand that Graves' disease is not an acute, but a chronic affection necessitating, so to speak, chronic treatment of sufficient duration to overcome not only the syndrome, but, as far as possible, the predisposition as well.

Having discussed the guiding principles underlying the nonsurgical management of Graves' disease, we shall in the next chapter discuss prophylaxis.

CHAPTER XX

PREVENTION OF EXOPHTHALMIC GOITER

If the profession were to become half as serious in the study of the prevention and cure of Graves' disease as in the study of tuberculosis, not only would many cases of the disease be averted, but surgeons, satisfied that internists can demonstrate excellent results, would refuse to operate on these patients.

Principles Involved.—The study of prevention of any disease must begin with an investigation of its etiology. While in Graves' disease we do not know of any specific cause or causes lending precision to our task, we are cognizant of a series of etiological influences, which, if at least partly eradicated, would mean much to the world at large. Attempts at correction of predisposing factors and the prevention of exciting causes mentioned in the chapter on pathogenesis under the heading of the neuro-endocrine theory, are the principles involved in the prevention of exophthalmic goiter. Though it is understood that despite concerted efforts at prophylaxis there will continue to exist many instances of the disease, a material reduction in the number of cases will amply reward us for our efforts. The *ideal* status would be reached only if a generalized simplification of human life were possible. Meanwhile, the march of civilization will be associated with many victims of Graves' disease.

Correction of Predisposing Factors.—An examination of the etiological factors under the neuro-endocrine theory will reveal the fact that many of them are amenable to corrective influences. Prophylaxis should consist of endeavors so to plan the individual's attitude and conduct with relation to the world at large as to fortify the bodily forces against Graves' disease. Presented with the opportunity of a free hand in the management of a young person born into a Graves' disease family, what can prophylaxis do to reduce or eradicate this susceptibility? The answer is obviously to avoid or circumvent acquired predisposing factors. The task is a difficult one; guidance must be perpetual, or at least up to well established adult life; but if it is done to within 50 percent of perfection, the incidence of Graves' disease would probably be reduced by 75 percent of the existing figure.

Every physician knows that an infant is rarely brought up in a way consistent with perfection in hygienic, dietetic, and mental management. Nearly always there is a degree of error varying from apparently

unimportant trifles to gross carelessness which often makes us wonder how the infant can survive the "fond" parents' care. Now, if one or both parents happen to be susceptible to, suffering with, or recovering from Graves' disease, we have in the offspring an instance in which hygienic, dietetic, and mental care *must* approach the ideal. To permit the baby to "just grow" is to invite a strong predisposition or inflammability to Graves' disease. For safety's sake, such children should be regarded as pre-Graves' disease subjects and as such, the object of prophylaxis from the very beginning. The most important suggestion to parents should be the matter of not accustoming the child to flesh food. Parents are apt to consider flesh food as necessary to the attainment of growth and strength, and may begin administering steaks, chops, and the like at the early age of 12 or 18 months. This is the first gross and most important error that could be committed.

When school life is begun, other factors become operative. Mental impressions from teachers, classmates, companions, relatives, and even parents may diminish or increase susceptibility to the disease, depending upon whether they approach or recede from the ideal. The quality and frequency of indulgence in recreation, whether this be at home, out of doors, or in assemblies at theaters, halls and the like, play their part with a potentiality that is not sufficiently appreciated. The "movies" are a most powerful factor in molding the mental health and character of young America.

During puberty and adolescence, added recreational factors arise, in that contact with the opposite sex tends to increase the existing emotionalism and mental disquietude almost and at times to the point of irrationality. In this category may be mentioned parlor games, inappropriate stage performances, and dance halls. An attempt must be made tactfully to avert these errors. Overambition in school and college duties and in the preparation of a career should likewise be under control. Females with a predisposition to Graves' disease must obtain complete physical and mental repose during the menstrual period, since menstruation is interrelated with the neuro-endocrine system, which latter is in a state of varying degree of excitability at this time. Irritability, hot flushes, weakness, emotionalism, outbursts of hysteria and temper are commonly seen prior to and during menstruation. Also, at this time, a distinct temporary hyperplasia of the thyroid gland with unmistakable though mild evidences of Graves' disease, may assert themselves. In girls and young women engaged in active pursuits, this bit of advice may be difficult to follow; but when regarded in the light of serious future events, a mutual understanding on this subject is usually reached without much ado.

It is during early adult life that the greatest peril exists in persons predisposed to Graves' disease, in that faulty dietary, social, sexual, vocational and other factors may intensify susceptibility to the utmost.

Dietary and related habits which tend toward an increased intake of toxins (and here the habit of constipation may be included), place a great strain upon the detoxicating organs of which the endocrines, especially the thyroid, are a part. These patients are often passionately fond of meats, frequently taking large quantities more than once daily. This habit may be discouraged by a conversation with the subject, with an explanation of the why and wherefore. I am frequently told by patients suffering with the disease that unless they take 3, 4 or more cups of coffee daily, they are at a loss to know what to do. The history of such a person indicates that the patient has been a slave to coffee and tea for years. Here, too, an explanation to the effect that coffee and related beverages are partially the cause of the illness, and inimical to a favorable progress toward health, usually results in satisfactory coöperation, and the error is eradicated. The same, in essence, may be stated of the various spices, condiments, and other harmful substances of food and drink.

One of the most difficult problems facing the internist is the prohibition of tobacco in persons addicted to its use for many years. Extrasystole and the various cardiac arrhythmias and even auricular fibrillation are more commonly seen in tobacco users of this class of individuals than in others. Unless the habit is stopped at once, all other efforts to assist our subject will prove fruitless. It is my custom to have the patient promise faithfully at the first visit never to touch tobacco again. I do not permit him to say "I'll try" or "I'll do my best," much less do I permit a gradual weaning away from the weed. Anything less than "I shall" implies effort with a minimum of determination and is a poor psychological procedure; "I shall" is usually successful; the patient stops using tobacco, and that is all there is to it. I frequently explain that a part of the tobacco habit consists in giving the muscles of the mouth something to do; the taking of chocolate coated nuts, chocolate peppermints, or crackers, when the craving for tobacco arises, will accomplish the same purpose, and these substances, being nutritious, will at the same time improve weight and increase strength.

Though a goodly percentage of predisposed individuals possess normal weight, and a few are to a degree obese, most are undernourished. These subjects require an avoirdupois to correspond at least to their height and age. Indeed, a 10 percent. increase in weight above the person's standard is highly desirable. The surplus serves as a safety point representing an amount of reserve to be relied upon in case of emergency stress and strain. These subjects are commonly poor eaters, though the appetite may be good or excessive. Many have sharp hunger several times a day, but it is quickly satisfied, unsustained and capricious. Thus in response to hunger, the intake of food is equivalent to one half the customary meal, and this, repeated throughout the three meals per day, corresponds to a smaller daily intake than that of the

average individual. Even an occasional "bite" between meals does not yield the number of caloric units required by a person of similar age and stature. The patient has accustomed the stomach to hold comfortably just so much and no more at a sitting, as a result of which the taking of a normal quantity of food causes discomfort. Correction should aim at persistent endeavor to accustom the organ to take at least a normal quantity of nourishment daily, irrespective of discomfort and other apparently undesirable consequences. In the course of several weeks of forced feeding, the subject finds himself eating plentifully, the weight reaches normal and soon above normal, and the 10 per cent. excess, our goal, is attained. A proper stomach capacity is now permanently fixed, and the weight is indicative of a more normal resistance to physical and mental emergencies.

The question of occupation is frequently a serious one. Aside from possible physical deterioration resulting from the pursuit of certain occupations associated with undue physical exertion, poisoning by lead, phosphorous, arsenic, mercury, and various noxious gases and impurities, there are occupations in which mental strain is a vital factor. Telephone operating with its nerve-racking incidents, school teaching with its well known potentialities for restless working hours and quite as restless hours off duty as a consequence, social work among the poor and suffering with its depression—these pursuits, though in the abstract the choice of the persons whose lives are devoted to the work, still carry with them very deteriorating influences upon body and mind. And if we take into account the numerous instances in which the occupation of an individual, such as manual labor, salesmanship, stenography, housekeeping,¹ and divers other pursuits forced upon the person in question, and far from being a pleasure, are a perpetual drudge and torture to life, especially the cases in which there is too little leisure and too much work, we can readily see how important is an investigation of the influence of the daily duties of the person under our study. Here we must not ignore the occasional unfortunate case of the man or woman "of leisure" who has become overly introspective for lack of something else to do. Lastly, there are a few occupations which, though not a drudge to the person in question, are associated with the possibility of acute mental or emotional strain, which possibility may serve as the sword of Damocles. Among these may be mentioned employment on the topmost floor of a tall building with its possibilities of fire or elevator accidents, employment in locations where explosions are possible, as in or near chemical laboratories and munitions plants, and others of like nature. Our task must entail an attempt at elimina-

¹The housewife often presents a problem all her own. Especially is this true in the presence of children and in the absence of a servant. The manifold duties of kitchen work, rearing the children, house cleaning and the like, with almost no out-of-door air or social existence, are potent predisposing factors of Graves' disease.

tion, or at least a reduction of occupational faults which interfere with the maintenance of an equilibrium between internal bodily conditions and external circumstances.

An ominous subjective symptom in this class of individuals is persistently unrefreshing sleep with or without disturbing dreams. A person of this sort frequently arises in the morning feeling not refreshed, rested, and ready for the day's work, but fatigued, weary, and anxious to remain in bed, irrespective of the hour, and caring little for breakfast. Such a status, occurring daily and prolonged for months or years, is a strong predisposing factor in the development of Graves' disease, and should be overcome by sane, persistent remedial measures calculated to induce healthful, refreshing sleep for at least eight out of twenty-four hours. It may be discovered that nine and even ten hours of sound sleep daily are required in order to secure the necessary physical and mental well-being. In this respect every person is a law unto himself, and the peculiarities of each subject must be investigated and evaluated without any hard and fast adherence to conventional standards. In general, the patient with a known predisposition to Graves' disease should be encouraged to devote an *extra* hour or two each night to sleep or relaxation, for the purpose of reinforcing the autonomic and endocrine stability against possible disturbing influences through the waking hours.

The strenuous life of the times—the mad rush to earn the dollar and the equally mad tear to spend it—coupled with the tendency in some quarters to illicit affection and its implications—all these and allied factors cannot be ignored in the consideration of causal relationship and the prophylaxis of Graves' disease. In the description of the neuro-endocrine theory certain earmarks of susceptibility to Graves' disease were enumerated and discussed. All such persons, especially if presenting a significant history, should be regarded as pre-Graves' disease patients, the object of prophylactic measures.

Were a careful sexual history made as a routine procedure, very valuable information would be elicited, facts which are otherwise missed to the detriment of the patient. Often we find that the sexual perturbation of puberty and adolescence, and indeed the thyroid hyperplasia, are continued indefinitely on into adult life. In both sexes, the sexual and emotional restlessness should be tempered by appropriate social, emotional and esthetic influences. The status of being affianced, marriage and pregnancy, in addition to the general sexual thoughts of the individual, are subjects which cannot be overestimated in this respect. It is here, perhaps more than elsewhere in the consideration of the prophylaxis of Graves' disease in the adult female, that common sense and vigilance should be exercised.

Faulty mental habits are almost the rule in these subjects. Aside from those already implied, temperament or disposition must be so influenced as to approximate the ideally consistent as closely as possible.

Many possess an undue hypersensitiveness; they are "thin skinned" and often pessimistic. Though high colored in attitude when things are to their liking, trivial difficulties and obstacles may turn tables so completely that moodiness, gloom, tears, and even hysteria prevail. To change this vacillating mental make-up into one of dependable stability, permeated by a healthy quality and quantity of optimism, though a difficult task, can at least in part be accomplished through the subtle influence of tactful friends or relatives, or under the guidance of a capable mentor. How to increase the threshold of emotional reaction is the vital problem. The substitution for a state of emotional alertness or *qui vive* by an attitude of *sang froid*; in other words, the assumption of the so-called phlegmatic temperament by one to whom every mole hill is a mountain, is the "consummation devoutly to be wish'd."

Though the prevention or reduction of the predisposing influences of Graves' disease may appear an abstruse affair, vague in its deductions and in many instances difficult of conception, much can be done by an inculcation into the individual of principles which, in course of time, would diminish discord and increase equilibrium between inherent peculiarities and susceptibilities on the one hand and controllable habits and environments on the other. An adherence to the broad principles of the *simple life*¹ and the discovery and fortification of weak links or vulnerable points in the subject's make-up, with an eye to individualization, will finally bring about the desired equilibrium in sufficient degree to be highly gratifying to all concerned. Having attempted the achievement of this objective, the next consideration is the avoidance, as far as is in our power, of the known exciting factors.

Prevention of Exciting Causes.—If in most persons with a susceptibility to Graves' disease we can prevent the occurrence of an exciting factor, the chances are highly in favor not only of the enjoyment of relatively good health, but also of unusual longevity. These persons, for some unaccountable reason, are known to exceed the span of three score and ten, and occasionally approach and even reach the century point.

Occupational, economical, and social exciting causes are due partially to the trend of the times and partially to fortuitous individual circumstances or inherent inaptitudes. These latter are amenable to favorable modification, but it is confessedly a difficult task if attempted after the ingrained habits of adult life are formed.

The sexual life of the individual must again be stressed as bearing an important relationship to the neuro-endocrine make-up of the individual. Sexual neurasthenia, priapism, and impotence in men, and in women prolonged engagements, sexual incompatibility, vaginismus, sterility, multiple pregnancies, and allied conditions are potent exciting causes

¹The best place for a subject of this type to reside is away from the seashore, preferably in the country, and at moderate altitude, a place where the simple life most likely characterizes existence.

and largely amenable to prophylaxis, depending upon the tact and skill of the medical attendant. In this regard the physician must be equipped not only with a knowledge of medicine but he must be capable of assisting his charge through a subtle application of practical psychology and through a knowledge of both concealed and revealed human nature. It is just here that the services of the medical attendant, depending upon his equipment, are either useful or futile. He must be in position to "father" his charge, and see that the crises of his or her existence are safely passed.

Earthquakes, lightning storms, tidal waves, and other natural phenomena which may engender cases of Graves' disease are beyond human effort to control. War conditions, conflagrations, explosions, elevator accidents, shipwrecks, massacres, automobile and train accidents, and other conceivable situations associated with danger to life and limb are largely man-made, hence at least partially avoidable. Unfortunately these conditions are not in the power of doctors or psychologists materially to control, and therefore not markedly amenable to their prophylactic efforts. It is reasonable to assume, however, that even if exciting causes cannot be averted, if we succeed in reducing in a given subject the degree of susceptibility to the affection, the onset of Graves' disease may be prevented.

Such occasional exciting causes of Graves' disease as local or general infections, autointoxications, pelvic neoplasms, and the ingestion of iodin or of thyroid extract are to be managed according to indications. As remarked elsewhere in this book, assuming that a focal infection is the exciting cause of a given case of Graves' disease, having begun the syndrome, its removal will have little if any influence upon the already established disease. In this respect, we might compare the removal of causally related badly diseased tonsils to the course of an already existing rheumatic fever. Despite these facts, however, infectious foci must be eliminated.

The prophylaxis of Graves' disease must also include a consideration of the prevention of relapse after recovery from an actual attack of the disease. In all patients in whom complete recovery has been firmly established and maintained for a year or longer, we may safely assume that the primary or fundamental predisposition to the disease has at least been materially minimized, if not altogether eliminated. This is especially true of patients in whom thyroidectomy was not depended upon, but who were fortunate enough to have been under the care of an experienced internist, with resulting approach to the normal or arbitrary standard of bodily and psychic health and the usual resistance to Graves' disease. Such a person, taught how to adapt himself to live in accordance with an "anti-Graves' disease" existence, is fully capable of fulfilling his function to himself and society at large.

Conclusions.—A review of the foregoing facts based upon the neuro-

endocrine theory of the pathogenesis of Graves' disease, leads us to the following conclusions:

1. Graves' disease is quite as preventable as tuberculosis; we have strong reasons to believe that in every case of Graves' disease there was a time when preventable measures could have forestalled the occurrence of the syndrome.

2. Ideal prophylaxis of Graves' disease should begin in infancy and extend well into adult life, the object being an attempt at perfection in hygienic, dietetic and mental discipline.

3. During childhood, such additional influences as school and home life, companions, recreation, and other factors capable of molding the physical and mental self must be taken into account.

4. During the restlessness of puberty and adolescence, the emotionalism, instability of reasoning processes, and the physiological thyro-gonadal hyperplasia, all make for an accentuation of neuro-endocrine instability and should receive most thoughtful, scrupulous guidance.

5. Predisposition to Graves' disease is not always markedly amenable to prophylaxis, nor are exciting causes of the disease always avoidable. In the absence of the ideal (the *eradication* of predisposing and exciting causes), if we can *reduce* susceptibility on the one hand, or *modify* the *chances* of the occurrence of exciting factors on the other, the prophylaxis of Graves' disease will have earned an important place in preventative medicine.

6. In general, an individual standard of conduct to self and the outside world must be formulated for these individuals. It is a two-fold task—each contributing equally to the achievement of the goal, *viz.*: (a) the adjustment or adaptation of the circumstances of life to the singular peculiarities of the individual, and (b) the modification and adaptation of the peculiarities of the individual to the circumstances of life.

7. Prophylaxis of Graves' disease by individual and organized effort is timely and important. The devotion of more time and energy by internists and general practitioners to the study of the diagnosis, prophylaxis and treatment of this affection would not only reduce the number of sufferers, but would promptly place the therapeusis of Graves' disease on a strictly nonsurgical basis.

CHAPTER XXI

HYGIENE IN THE MANAGEMENT OF EXOPHTHALMIC GOITER

IN this category we must eliminate all discoverable personal and environmental hygienic errors already discussed in the chapter on Prophylaxis. In addition, we shall include a consideration of rest, exercise, hydrotherapy, climatotherapy, gastro-intestinal hygiene, and mental hygiene.

REST

By the term rest in the management of Graves' disease is meant that state of body and mind wherein catabolic and degenerative processes are reduced to a minimum and anabolic and regenerative processes are enhanced. Rest aims at a reduction and elimination of that consuming overalertness or quickening of mental and physical processes characterizing the disease. To quiet and stabilize the circulatory tree, to overcome the excitability of the gastro-intestinal, genito-urinary, cutaneous, and other systems of the body, to reduce the oxidation of the tissues and enhance the restoration of bodily weight and strength, and, finally, to tranquillize the turbulent emotional status of the individual—this is the function of rest as a constituent of a broad management of Graves' disease. Rest as here qualified imbues the patient with a sense of complete repose which is the essential prerequisite to satisfactory results from other therapeutic measures. Finally, rest in the treatment of exophthalmic goiter is not necessarily a prolonged, absolute confinement to bed.

Absolute Rest in Bed, without respite, adopted as a general measure in all cases, is an erroneous procedure, as in many instances this tends not to rest the patient, but to increase introspection and excitability and aggravate the syndrome. Rest as above defined may be procured by certain *activities* outside of bed. This is not paradoxical, for any form of physical and mental pastime which does not increase, but rather diminishes the patient's overalertness, is indicated. Thus, for instance, a change from the monotony of bed and home by attendance at a lecture or a musicale, congenial conversation, and the like, would so modify the inner self of the individual as to conform with our definition of rest.

"Hibernation."—In summarizing the value of rest in his discussion of the "kinetic drive," Crile states: "If an individual with exophthalmic goiter could be made to hibernate like a bear, he would probably come out cured; for when the driving mechanism, the brain, rests, then the organism as a whole rests; and if the rest is long enough, certain pathological states tend to revert to the normal state." To hibernate by staying in bed, however, is not always to rest the brain. As a consequence, the body, too, is not resting. To hibernate is indeed what the patient requires, but the *method pursued* in the attainment of this state is what concerns us. Mistaken methods lead to disappointment. What is rest to one patient is irritation, indeed, hard work, to another. Individualization is of primal importance in this connection, as in all other branches of treatment of Graves' disease. With hibernation of body and mind in view, the expert internist must make a careful study of the individuality of the patient and the type of Graves' disease presented; and he must prescribe the method of procedure accordingly. It is the quality and quantity of rest that constitute individualization. Moreover, a prolonged, absolute rest in bed may cause a good digestion to become bad. We often see patients who have been kept in bed for ten, twenty or more weeks leave it in a worse condition than they were formerly. Patients may rest quite as satisfactorily by sitting in an armchair a few hours a day, and surely feel more comfortable and contented. Moreover, the patient need not be deprived of the pleasure of sitting at the family dinner table, and even of a slow, short walk in the open, the weather permitting. Such a régime of rest strengthens the circulatory and nervous systems, improves appetite, enhances digestion and nutrition, and tends to increase body weight more rapidly.

Rest in Patients with Cardiac Degeneration.—There is an important exception, however, to the remarks covering absolute rest in bed. In the presence of impending or actual cardiac decompensation, or in instances of auricular fibrillation, with a badly dilated heart with leaking valves, the general principles of rest as outlined must be ignored in the interests of a restoration of circulatory balance. This requires absolute rest in bed and other measures in accordance with the exigencies of the case. Following a satisfactory restoration of circulatory function, modifications in the rest program may be guardedly instituted.

Rest in the Average Case.—In the average patient, in the absence of serious myocardial difficulty, I advise the following outline of rest:

- 8 P. M.—Retire to bed.
- 10 P. M.—Extra nourishment in bed; sleep.
- 7 A. M.—Breakfast in bed.
- 10 A. M.—Arise; extra nourishment.
- 2 P. M.—Retire to bed.
- 4 P. M.—Arise; extra nourishment.

This gives the patient 16 hours in bed out of the 24, which is a sufficient stay in bed for approximately 75 percent of patients presenting themselves for treatment of Graves' disease. Depending upon the individual, from ten to twelve or more hours are spent in actual sleep. The remaining hours in bed are devoted to complete relaxation. The question of insomnia during hours which should be spent in sleep is discussed under medical treatment. Relaxation, that is, the stay in bed when not asleep, is something that must be taught these patients, as they do not understand what is meant by this term. "Relax your limbs so completely that you are not aware of their existence. Think of nothing at all; make your mind like a blank sheet of paper," is what I usually say to the patient when discussing the subject. This is usually understood; the patient enters into the spirit of the matter, and relaxation is successfully carried out.

The eight hours spent out of bed are devoted to restful pursuits of varying kind. Listening to music, reading light literature, pleasant conversation, engaging in light games, or looking out of the window if the scene is attractive, and various other pastimes may be found to while away the time pleasantly. If deemed feasible, and weather permitting, the patient may sit out of doors for two or three hours daily, or may even be permitted to take a short, slow walk in the open.

Duration of Rest Cure.—This program of sixteen hours in bed and eight out of it is continued on during the several months of active treatment required to affect a restoration of the normal pulse rate and weight. This accomplished, there is a gradual reduction in the number of hours spent in bed until finally, perhaps at the end of a year in previously serious cases, and in much less time in less serious cases, the patient need spend but 8 or 9 hours in bed at night and an hour or two in the afternoon. In the course of time, in patients in whom the cardiac mechanism is completely restored, no afternoon rest in bed is necessary, and the patient lives a normal existence.

Of course, if through stress of circumstances the patient must perforce stay out of bed longer than eight hours and must also perform some household duties, we are obliged to meet the situation half way and prescribe such a program of rest as will coincide with existing conditions. If despite adverse circumstances, the patient's condition demands more rest than can be afforded, the physician must insist upon having everything subserve the interests of recovery. Under such circumstances, assistance on the part of relatives or others must be enlisted and the necessary sacrifices made until the period of danger is over.

In a patient suffering with the *forme fruste* type of the disease, whose occupation is of sedentary nature, it may not be necessary to discontinue work if the duties attached are congenial. I have often succeeded in keeping such individuals at work during treatment. Progress is not as rapid as under ideal circumstances, the period of active treatment requir-

ing a few months longer, but the patient continues wage earning while under the therapeutic régime and makes satisfactory recovery.

WHERE TO REST

We have discussed the necessity for peace, tranquillity, harmony and other attributes, *pro* and *con*, as having a very marked bearing upon progression or retrogression in the patient's condition, as the case may be. Shall we keep the patient at home, or had he better be kept elsewhere during the weeks or months of trial? In the solution of this problem, the doctor must here again become somewhat of a sociologist and psychologist. He must evaluate not only apparent conditions, but factors beneath the surface as he discovers them. In so doing, he must take other members of the household into his confidence.

Shall the Patient Remain at Home?—To confine oneself to hard and fast rules in response to this question is to create obstacles. The patient's petty whims and notions and the various idiosyncrasies of his personality are easily brought to the surface, creating a state of discord, expressed or suppressed. The slightest like or dislike of the doctor, attendants, environments, even the very bed he lies upon and the very wall confronting him, to say nothing of the view outside the window, may so irritate consciousness as to engender or increase fretfulness and fractiousness.

Of course, psychotherapy here plays its part, and we shall discuss this phase of treatment elsewhere. But even attempts at mental adjustment must include the immediate environments of the patient. If the home is one in which everyone about him is eager and anxious to follow the doctor's orders religiously in the interests of the patient, if the members of the household are level-headed, capable of bearing with the many whims and apparent unreasonableness of the patient, if common sense and logic, not sentiment and emotion, dominate the household in the matter of coöperation, and if, lastly, the *patient* succeeds in adapting *himself* to this household, the home is by far the best place for our subject. To remove the patient under such circumstances may accentuate the manifestations of the disease. Homesickness, with its accompanying lonesomeness, the difficulty of adjustment to strange environments, the unaccustomed method of the preparation and serving of food,—these and other reasons should preclude the consideration of sending the patient away to a strange environment. A happy household, sane attention, congenial medical attendant, an affection not overstrained, with peace and tranquillity pervading the household, an ample social sunshine and an abundance of smiles characterizing the waking hours, make the home the ideal place for these patients. The creation of a favorable picture of this sort may require suggestions and

attention on the part of the guiding medical attendant, but whenever this obtains, the satisfactory progress of the patient is assured.

But what if the situation is the reverse, and there are perpetual frowns, discord, antagonism, friction, and interminable warfare, as is frequently the case? What if the household, including the patient, cannot be brought under the sway of the medical attendant in his efforts at peace and harmony; what if the very atmosphere has been the exciting cause of the Graves' syndrome? Then there is only one recourse,—to send the patient away to a more congenial atmosphere, where the turbulence of the emotions can be made to simmer down, and where finally peace may be restored within the patient through an adjustment with external circumstances. Where shall we send such a patient?

Shall We Send the Patient to a Hospital?—This is too frequently done without forethought. How often have I seen a poor patient sent into a mixed ward where the attention is cursory, the demeanor of the attending physicians, nurses and others is brusque and hurried, and where the individual's daily and uninterrupted vista is one of pain, suffering and groans! This sort of atmosphere makes for anything but improvement. Not only is there no actively interested person about this patient, no individualized diet, medication, and other necessary attention, but there is that negative atmosphere which accentuates the already existing syndrome. How often have I seen such a patient placed in bed for "observation" leave the hospital within a month or two, weighing much less than before, with an increased heart rate, and an increased turbulence of the emotional make-up! Were this a ward of an institution for the treatment of these patients only, and the medical attendants trained and experienced in the physical and mental management of this peculiar type of humanity, such a place would offer no objections. Indeed, the existence of such an institution would fill a long felt want, and would save many thousands of lives.

Of course, a person possessing the necessary means might take a private room in an ordinary hospital and there receive the necessary individualized attention, both medical and otherwise. This would be far preferable to a negative home atmosphere. Still, a hospital atmosphere cannot successfully be eliminated even under these circumstances.

Shall We Send the Patient to a Sanitarium?—Yes, if the place is one abounding in a congenial, homelike atmosphere, not approximating in appearance and tendencies the usual hospital. No, if the sanitarium smacks of the usual sick bed flavor, and if there are many persons about our patient who are in a helpless condition. Of course, a congenial sanitarium is a good place to carry out strict military discipline, other things being equal. But military discipline, though of vital importance, must be associated with that intangible something which makes for internal contentment in the patient. Unfortunately, there are very few sanitarians of the kind indicated for these patients.

Many of them are so-called "homes for incurables" or "homes for nervous people" which are other names for places of segregation for persons of unbalanced mind. Though a subject of Graves' disease may appear mentally unbalanced, he is nearly always amenable to mental uplift and restoration to the ranks of the sane, but this requires the contagion of a strictly sane, mentally healthy environment. So that the question of sanitarium, too, must be carefully considered ere conclusions are reached.

Shall We Send the Patient to the Country?—Here, again, we must qualify our remarks. If the patient is suffering with the early stage of the disease and has not yet presented evidences of damage to the vital organs and requires no intensive rest program, so that the services of a nurse, though desirable, are not imperative, my answer would be in the affirmative. A very sick patient, however, would, generally speaking, do badly in the country. The country is the place for healthy or nearly healthy people; an individual requiring intensive medication and nursing is out of place in such a locality.

Again, some "countries" are not fit places for anyone to go to. Either because of the persons conducting them, or because of the undesirable location, or both, a country place may be as bad as an unhappy home. Barring these unfavorable circumstances, however, a country place situated at a moderate altitude, say 1000 to 2000 feet above the sea level, with ample, soothing, invigorating landscape about, and the proper sanitary conditions and foodstuffs, as well as personal attention, prevailing, is excellent for a patient who is either suffering with the early stage of the disease, or, having recovered from its severe stage, is convalescent and requires a change of scene to emphasize or confirm recovery.

Shall We Send the Patient to Another Climate or the Seashore?—To send the patient off to another climate is usually unnecessary, unless the existing geographical location is obviously harmful to the case in hand. If, for example, the patient is in a perpetually hot climate, or at the seashore, or in an excessively damp atmosphere, it may be necessary to send him off to a picturesque, moderately elevated, cool, dry spot, possessed of an equable temperature. It is assumed, of course, that the necessary medical attention and nursing can be carried out while there. If not, the favorable influence of the new climate will not offset the harm of lacking medical attention.

With few exceptions, the seashore is, generally speaking, not an ideal place for patients with Graves' disease. Though I have seen a few patients thrive at the seashore, especially during convalescence, I have seen very many of them become worse whenever the shore is reached.

To summarize, then, we might state that the best place to keep the subject of Graves' disease (assuming that the proper régime of

therapeutics is available) is, first, the congenial home; next to this, a country place or even a sanitarium possessing the aforementioned virtues. Finally, after discharge from active treatment, it is always a desirable, though not a *necessary*, procedure to urge the patient to indulge in a favorable change of scene for a variable time. Thus, the individual, refreshed and rejuvenated, returns prepared and eager to resume a normal physical and mental existence.

EXERCISE

After a satisfactory degree of improvement is attained, exercise may be prescribed as the step essential to a restoration of the patient's usefulness.

Passive Exercise.—In a patient whose heart has been badly degenerated at the start, exercise must be postponed indefinitely, and the body must continue, as it were, to hibernate for yet a while. Such an individual may have *passive* exercise or massage prescribed in accordance with prevailing conditions until *active* exercise can be safely permitted.

Passive exercise in the form of mechanical vibration or massage may be given to all subjects of exophthalmic goiter. The vibrator, of a type run by a small motor, is easily procurable and serves the purpose very well. Moreover, vibration, if directed along the spine, particularly the cervical region, may induce a sense of well being through a sedative effect on the cerebrospinal axis. Manual massage exerts a similar effect, though not as promptly. Passive exercise should be administered lightly and for a brief while at first and gradually increased, depending on the results obtained and the mental attitude of the patient toward the procedures employed. The salutary efforts of passive exercise are often seen in the resulting calm, refreshing sleep.

Active Exercise.—In occasional instances idleness is etiologically related to the disease, for in leading to introspection it has caused the susceptible individual to become self-centered and paved the way for nervous instability which finally culminated in Graves' disease. Here exercise is indicated both as a prophylactic and as a curative agent, and it should soon acquire a character both stimulating to the body and interesting to the mind.

As the patient begins to tolerate and enjoy preliminary forms of exercise, certain calisthenic movements may be prescribed, care being taken not to invite fatigue. Patients having just recovered from Graves' disease are susceptible for several months to a flaring up of heart hurry and dyspnea on slightest exertion. This must be borne in mind in calculating the quality and quantity of calisthenics prescribed. In the course of a few months it will be found that a satisfactory amount of exercise may be prescribed without any extraordinary increase in

the heart and respiratory rate. Walking, which at first amounted to a fraction of a mile daily, may now be increased to two or three miles once or twice a day. Careful horseback riding and even leisurely boating are also useful forms of exercise. The various exercises with dumbbells or Indian clubs once or twice daily, follow in order, especially in younger patients. Apparatus work in the gymnasium must be permitted cautiously and after due consideration of every detail of the patient's condition, and must be indulged in only under the complete guidance of a medical attendant or nurse. It is better to err on the side of conservatism than to court a return of the tachycardia. Incidentally, piano and violin playing are desirable forms of exercise and serve as recreation. Patients who have already studied one or the other instrument may resume practice with moderation at an early date.

Exercise to Be Avoided.—Such forms of exercise as bicycling, baseball playing, or tennis are too violent and exciting, and should not be indulged in for a few years. Assuming that there are no heart complications, I do not permit roller- or ice-skating until a year has elapsed from the time of discharge from active treatment. Golf, and a moderate amount of swimming, may also be permitted at that time. Careful automobiling with the patient seated passively observing the scenery is permissible, but the patient must not drive the car, more especially if it be a high-powered machine on a busy thoroughfare. The temptation to speed is too great even for one who has never had Graves' disease. Again, it must be recalled that in recent years a large percentage of patients of Graves' disease have automobile accidents for their exciting cause. I have seen many instances in which the clandestine driving of an automobile by a patient who should have been resting in bed ended disastrously. Also, I have seen patients who, after having progressed most satisfactorily during the first few weeks of treatment, suffered a severe relapse through the added shock of an automobile accident. To illustrate, I might mention the case of a young professional man in whom, after several weeks of observation, I found none of the customary evidences of improvement. Suspecting lack of coöperation, I quizzed him rather carefully but could elicit no information pointing to the reasons for lack of progress. The following week he called on me in a state of extreme excitement and stated that he had just driven his car against a post in order to escape killing a pedestrian. His car, which he was driving at high speed, was wrecked, and he narrowly escaped with his life. On further inquiry, he confessed to utter disregard of all instructions. It was evident that here we were dealing with a case of complete insincerity.

Pulmonary Gymnastics.—Deep breathing should be taught the patient and he should be encouraged to practice it throughout life. If we recall the fact that in exophthalmic goiter there is a diminution

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of respiratory expansion, and also that in these patients there is occasionally a latent focus of tuberculosis, or a strong predisposition to this disease, we must conclude that the value of pulmonary gymnastics cannot be overestimated. Deep breathing may be begun in all cases, however serious they may be. In the advanced form with cardiac embarrassment, the patient is instructed to try to breathe just a little more deeply than usual, and twice a day, night and morning, to take 10 or 20 deep "sighs." This will serve the purpose at first. In the average case, in addition to instructions to throw the chest forward and the shoulders backward and to inculcate a deep breathing habit, the patient is ordered to take a deep breath to within the point of discomfort. A cracking of the usually unexpanded portions of the lungs will be felt and heard. The breath is held for a second or two, and the process of expulsion is begun and continued to the point of discomfort. After a second or two, the excursion is repeated. Twenty or 30 such cycles should be practised each night and morning, either in the open or before an open window. There is not only a beneficial local effect in the lungs, expanding and strengthening areas heretofore flabby and semi-diseased and rendering them less liable to infection, but there is a general beneficial effect, improved vasomotor stability, increased appetite, and an improvement in nutritive balance.

In concluding these remarks on exercise in the candidate for discharge from active treatment of Graves' disease, we must not forget the mental factor involved. Mental exercise is quite as important as physical and must be prescribed with quite as much discretion. This is further discussed under psychotherapy.

CLIMATOThERAPY

The subject of change of climate has already been mentioned. We may reëmphasize that, in general, climate is not an important consideration in the management of exophthalmic goiter. As in hay fever, asthma, nephritis, chronic rheumatism, and other morbid conditions, so in exophthalmic goiter, we find that a climate which benefits one patient may not benefit the next. One patient may feel better at the seashore, another in mountainous districts, still another will find improvement in Florida or in Canada. Generally speaking, it has been found that patients fare badly at the seashore. We must individualize here as elsewhere, and take into account not only the existing physical conditions, but also the patient's peculiarities and idiosyncrasies. All things being equal, the patient being accustomed to his or her home climate, had better not change. In the presence of satisfactory coöperation on the part of the household, it is safe to conclude that home climate, home faces, home-made meals, and continued home attachments are far more conducive to desired results than a strange,

untried climate, strange, indifferent, and possibly insincere faces, and strange, often questionable meals. However, where the home is conducive to oppressive monotony or there exists unpleasantness or friction between the patient and the members of the household, a *change of scene* is highly desirable and often of vital importance.

HYDROTHERAPY

In exophthalmic goiter, though hydrotherapy is a useful adjuvant to other measures, it possesses no special virtues. A daily lukewarm cleansing bath is of course to be advised in every case; the vasomotor instability of the periphery is thereby improved, and hyperidrosis is benefited. There also occurs a general sedative effect on the heart and nervous system, especially if the bath is taken at bedtime.

A cold sponge in the morning may be relished by some patients and disliked by others. The aversion to cold water bathing had better be heeded in the average case. However, the application of cold to a very vascular hyperactive thyroid gland and to a turbulent heart is a valuable procedure; this is accomplished by the use of ice bags or the Leiter coil. The slowing of the heart rate is very gratifying to the patient and the restlessness is considerably reduced.

The drinking of an ample supply of cold, sterile water should be encouraged. Although in many patients the thirst is excessive, keeping pace with the hyperidrosis and polyuria, in some instances the subject does not imbibe the necessary quantity, as a result of which the functions of the emunctories are hindered and the emaciation becomes more marked than ever. These patients should therefore be encouraged to take plenty of fluids in the form of milk, buttermilk, and an abundance of water.

GASTRO-INTESTINAL HYGIENE

This subject is discussed in detail under the dietetic treatment of exophthalmic goiter. The mouth must be freed from focal infection. Decayed teeth, pyorrhea alveolaris and the like must be attended to at once and in an expert manner. In addition to the proper use of the toothbrush, the patient must be advised to use a mild antiseptic mouth wash and gargle two or three times daily, and oftener if necessary. Food must be "Fletcherized," and all mental tension must be guarded against during mealtime. A funny story, congenial companionship, and other circumstances of like nature, enhance appetite, improve digestion, and make for general improvement, especially of the circulatory and nervous phenomena. After food is taken, an hour's rest in an armchair, during which the mind is entertained by light reading, pleasant conversation, light table games, or appropriate music, may be followed either by a nap or a slow walk, as indicated.

The bowels must be kept in good functional condition; diarrhea or constipation, as the case may be, must be managed according to individual indications.

MENTAL HYGIENE

Mental hygiene has already been implied in the paragraph "where to rest" and is further discussed under psychotherapy. It need only be stated here that all factors conducive to a state of excitation of the emotions are promptly to be eliminated. This concerns not only intrinsic factors such as doubts, suspicions, obsessions, business cares, religious, marital, or sexual matters, but also the various extrinsic factors, as false friends, unsympathetic parents, noisy children, curious neighbors, a jealous, scolding helpmeet, an insipid, unbearable relative, and even stubborn creditors,—all of whom maintain a state of discord or friction between internal relations and external circumstances. The importance of a proper understanding of the patient's psychic construction by the doctor and the attendants, and the institution of the necessary psychological methods in efforts at a restoration of the patient's nervous stability, are highly advisable circumstances in the management of these cases.

CHAPTER XXII

THE DIET IN EXOPHTHALMIC GOITER

PRACTICAL dietetics is a much neglected subject. There is a great lack in the understanding of the therapeutic value of food. In everyday practice the subject of diet is usually dismissed with a sweep of the hand; an order to eat less of this or more of that is briefly given by the average physician to his patients, and nothing more specific is said. The fact of the matter is that there are many patients, ambulatory and otherwise, whose indisposition is due to improper quality and quantity of food, whether the patient or physician knows it or not, and a correction of diet with or without medication would make for quick recovery. I have observed in some instances of Graves' disease that the diet is at least a predisposing etiological factor in the production of the syndrome. It is unnecessary to go deeply into the theoretical side of dietetics and discuss minute details in caloric values. A practical knowledge of the subject, with as much attention to the food as to the writing of a prescription, is all that is required.

There are three sources of criticism of the attitude of the usual medical management of Graves' disease with regard to the dietary question: (1) A total indifference to the question of diet in Graves' disease, in which the patient is permitted to shift along upon his own initiative; (2) the tendency to place the patient on a liquid diet, especially milk; (3) a recent tendency on the part of a few observers abroad to place the patient on a starvation régime somewhat akin to the Allen treatment in diabetes; and (4) the placing of the patient upon an excessive meat diet.

Indifference to Diet.—Even more than in tuberculosis, diabetes mellitus, and other diseases where the destructive metabolic processes overbalance the constructive forces, in exophthalmic goiter an adjustment of quality and quantity of food and the regularity and frequency of its administration are essential to a restoration of the nutritive balance. To assume an attitude of total indifference to dietetics in Graves' disease and to permit the patient to take the path of least resistance is to neglect a vital element in the therapeusis of the disease and to invite failure. *The lack of attention to the proper dietary is one of the main reasons for the failure of most internists in the management of Graves' disease.* The diet of these patients must receive as much

thought and attention as all other measures employed, and success attends efforts in which feeding is a main issue.

The Liquid Diet.—The placing of these patients on a milk diet exclusively as a routine procedure is a mistake. That a milk dietary is not a desirable means of maintaining the body weight is seen in the fact that even in typhoid fever it has been abandoned in many quarters, with happy results. What are the objections to the so-called milk diet? (a) Many patients possess a natural aversion to milk; (b) it becomes monotonous in time to nearly every patient; (c) it is not really a "complete" food for adults, which fact leads to an increase of the existing emaciation already being carried on by the existing toxemia, thereby reducing the patient's resistance to a minimum; (d) hard, cheesy curds resulting from the ingestion of milk are largely responsible for the irritation of the gastro-intestinal mucosa, fermentative processes, tympanites and diarrhea; (e) a prolonged milk diet renders the digestive processes so delicate as to lessen their ability to digest other foods. This last factor explains why patients under a milk diet, when given more liberal feeding at any time during the course of the disease, fare badly and often present evidences of digestive disturbances. It is necessary to administer more than 5 quarts of milk daily to furnish a sufficient number of calories to maintain a normal person's nutrition. This quantity of milk is practically impossible for a person in health or disease, so that if the milk diet is insisted upon, the patient is slowly starving while combating a prolonged illness requiring an enormous quantity of food as a condition to recovery.

Milk is a very useful food, *as a supplement to a varied or mixed dietary*. The same is to be said of the continuous milk and egg dietary which, formerly so popular, is now happily falling into disrepute as a cure-all in conditions requiring an abundance of nourishment. Milk and eggs are highly useful adjuvants or supplements or constituents of a varied dietary and serve to fulfill all the requirements of food to be employed for supplementary forced feeding. But to employ any one or two articles of diet to the exclusion of all the rest fails in its purpose in the great majority of cases. Other elements of a liquid dietary such as broths, beef teas, and the like, contain little, if any nutritive value and are highly objectionable because of their stimulating properties.

Starvation Diet.—Several observers have recently advocated the starvation treatment for patients with Graves' disease, somewhat on the principle of the Allen treatment in diabetes mellitus. It is only necessary to examine a few clinical facts to note the absurdity of starving these patients. The great loss in weight and strength in Graves' disease is due largely to the increased oxidation occurring within the tissues,—the proteins, carbohydrates, and fats. In addition, the symp-

toms of indigestion,—the anorexia, nausea, vomiting, diarrhea, polyuria, and hyperidrosis further reduce the body weight through a diminished assimilation of food and the great loss of fluids. The increased metabolism of nitrogen, calcium, sodium and phosphorus, the increase in urea and uric acid, an increase of approximately 60 percent. of CO_2 from the lungs, the glycosuria,—all these attest the presence of widespread, practically universal destruction of tissue occurring in these patients. Boothby and Sandiford, in a quantitative study of the food intake, urinary elimination, blood chemistry, and the respiratory metabolism in exophthalmic goiter, found the total metabolism to be frequently in excess of 5000 calories per day and occasionally over 6000 calories, which is in marked contrast to the daily food ration of 1500 to 1800 calories common in many countries during the war. A recognition of these facts will carry us very far in the recognition of the dietary treatment, and to say that further starvation is unscientific is putting it mildly. A procedure may be unscientific and yet harmless to the patient, but deliberate starvation in Graves' disease is the most harmful thing that can happen to the patient, excepting perhaps the administration of thyroid gland. And yet, Tallquist, Curshman, and others, basing their conclusions upon observations made during the World War, state that inasmuch as food is a stimulant to metabolism and since in exophthalmic goiter the basal metabolism is already high, starvation is the logical treatment of this disease. This method of treatment is not only impracticable and based upon erroneous assumptions, but dangerous. The only possible relationship I can see between starvation and exophthalmic goiter is a sinister one, *i.e.*, starvation is occasionally an etiological factor of the disease. An analysis of patients observed under a starvation régime (and I have seen a number of them) indicates that this treatment, increasing emaciation and weakness, aggravates the entire syndrome of the disease, rendering the prognosis graver than ever. In the occasional instance of apparent improvement in basal metabolism from undernutrition, it was not starvation which helped, but the *enforced physical and mental hebetude because of extreme weakness consequent upon starvation* which led to a lowering of the pulse rate and a tiding over of a catabolic crisis. But this result need not depend upon such strenuous means. Superalimentation and obedience to prescribed physical and mental rest yield far more satisfactory results. A loss of weight in exophthalmic goiter is always a bad omen. The outcome of a case of Graves' disease is good only in proportion to the amount of weight gained. Though it is true that increased food ingestion means an increased metabolism and starvation a decreased metabolism, we must really recall that the lowering of the food intake and of anabolism, with gradual lowering of bodily activity, may be carried on until, through sheer exhaustion, the corpse is reached, with a total absence of food

intake and of metabolism. A lower basal metabolism during starvation is due to a lessened burning up of *food*, not of bodily tissues, and, though the basal metabolism is lessened in the starving sufferer from exophthalmic goiter, there is a relative increase of burning up of the patient's own *tissues*. This explains why hospitalization of average patients with Graves' disease is a failure. They starve on a hospital diet, when, in truth, they should be taught to become gluttons. Super-alimentation, again, is a vital need because the patient requires the food to take the place of his own tissues which are being consumed by the morbid processes of the disease. During forced feeding the fires of metabolic processes play more upon the *food* ingestion and less upon the patient's tissues. Soon the results of the rest and other measures prescribed are manifest; the basal metabolism is genuinely reduced, with anabolism assuming the upper hand, and the patient, instead of being a shadow of his former self, is well on the way to recovery. It is not starvation, but the extreme of forced feeding plus a prescribed rest of body and mind that constitute the essence of successful treatment of Graves' disease.

The Meat Diet.—The diet in exophthalmic goiter must contain a minimum of animal food. This is attested by laboratory and clinical observations in this country and abroad. Leo Loeb, for instance, after feeding meat to guinea pigs, discovered that there occurred thyroid hypertrophy in three weeks. The preparation of a well-balanced meatless diet, including all the essentials of nutrition, is not a difficult task and must be seriously undertaken for all patients suffering with exophthalmic goiter. A non-flesh dietary is not synonymous with a vegetarian dietary, since milk, eggs, butter, and the like, though animal foods, are not only permissible but constitute important items in the menu. Meat is *not* necessary to physical and mental well being. On the contrary, it impedes vigor and shortens life. In taking flesh food, we take food, indeed, but *food plus the poisonous waste products* which the animal is about to eliminate prior to its death. We cannot take flesh food without its poisons. It may be well enough for comparatively normal persons to cope with these poisons added to their own, but the subject of Graves' disease is already badly poisoned by the diseased process, and to give him flesh food is analogous to giving him more poison. Moreover, the intestinal flora of flesh eaters contains a maximum of pathogenic organisms. Flesh eaters are more apt to suffer from digestive difficulties, and extra nourishments are tolerated with difficulty. Flesh food stimulates metabolism to a greater extent than any other food. Hence, since in exophthalmic goiter we are dealing with an excessive metabolism, further stimulation by flesh food is distinctly *contra-indicated*.

On the other hand, a non-flesh dietary, fresh and properly prepared, contains no harmful poisonous waste products; it is relatively

free from pathogenic organisms and parasites; constipation and auto-intoxication are rare; the digestive faculties are not hindered; extra nourishments are soon taken with ease; and the basal metabolism is not stimulated by an excess of purin bodies. Strangely enough, most exophthalmic goiter patients are excessive meat eaters, and it may be difficult in some instances suddenly and completely to withdraw all flesh food from the dietary.

The Patient's Weight.—One often inquires why, in otherwise normal individuals, one person, eating but a small quantity of food daily, retains an excess weight, while another, consuming perhaps two or three times as much food, remains thin. With few exceptions, the thyroid and other endocrines seem to play no part in the phenomenon. It is the so-called "metabolic temperament,"—the specific nutritional status characterizing the individual. There are no rigid natural laws of nutrition and metabolism. Though generalizations obtain for the average man or woman, exceptions constitute a large percentage of those under our daily observation. Aside from individual peculiarity or "metabolic temperament" as an explanation, we might advance the following reasons for this phenomenon: (a) Insufficient mastication, resulting in deficient utilization of food ingested and the expulsion of undigested food from the bowels. (b) Ingestion of an excess of protein, especially in the nature of flesh food; this stimulates metabolism, with resulting catabolic excess. (c) Physical, mental, and emotional hyperactivity, which not only utilizes an undue quantity of energy in many persons, but also requires a greater food intake because of the whipping up of metabolism. These instances are not related to Graves' disease, excepting in so far as undernutrition may increase susceptibility to the affection.

A patient who starts out at the inception of Graves' disease as an obese individual is one in whom the course and prognosis will be favorable. The reason is that natural corrective forces, on the alert to adjust erroneous processes, may begin to assert themselves in advance of an actual appearance of emaciation. Especially is this true if the patient is fortunate enough to be placed under a timely rational régime of therapeusis, in which case there is no difficulty in obtaining prompt recovery.

In some instances of mild form in persons not undernourished at the outset, there may be observed an increase rather than a decrease in weight. This is due to the enormous appetite and corresponding intake of food—an effort on the part of Nature to compensate, resulting in overcompensation of the abnormal catabolic processes incident to the disease. Thus we have the apparent paradoxical clinical picture of an outspoken Graves' disease plus a tendency toward moderate obesity. This natural overcompensation is observed only in patients who happen to be almost or complete abstainers from

fleshy foods—a class of patients responding promptly to treatment.

A patient beginning with the conventional normal weight is less fortunate, for Nature is usually incapable of curbing the morbid processes of the illness, excepting in cases in which spontaneous recovery asserts itself. Ordinarily, such a person goes through the serious course of the illness and its manifold intercurrent conditions and complications. But, placed under a timely régime of proper remedial measures, under the guidance of an individualizing internist who understands this work, recovery, though an uphill struggle, is highly probable in course of time.

A subject of Graves' disease who did not possess the conventional normal weight at the onset of the illness, but who was undernourished prior to that time, is rather unfortunate. It is from this class of individuals that many instances of resistance to treatment are seen. A delay in treatment in a patient of this sort frequently leads to disaster. Having started out on a prolonged career of further emaciation, it becomes a difficult task to effect the increase of the vital resistance necessary to the restoration of health. However, here, too, a carefully applied régime of treatment and faithful coöperation means recovery in the great majority of instances.

Quantity of Food Required.—The qualitative aspect of the diet has already been mentioned. Quantitatively, the outline of diet must take into account the following points:

- (a) The amount of food ordinarily required by a normal person of same sex, age, and height.
- (b) The amount of food necessary to neutralize the excessive catabolic activities of the disease, so that further loss in weight will cease.
- (c) The amount of food necessary to regain the loss of weight already incurred during the course of the affection.
- (d) The amount of food necessary to effect a 10 percent. excess over and above the patient's normal standard of weight, as a requirement at the time of discharge from treatment.

An examination of the requirements of (b), (c) and (d) will lead to the conclusion that, roughly speaking, a patient of this type during the course of the disease requires from 100 to 150 percent. more food daily than a normal person of similar age, sex, and height. To administer a *normal* quantity of food to such a person means a continuance of the disease and its emaciation, since the excessive catabolic processes continue burning down the tissues. These patients require far more food than those who are hard at work, and if, as was pointed out, the disease process itself is capable of utilizing 6000 calories per day, it is obvious that *forced feeding* is the only dietary salvation for these patients. We must insist upon the ingestion of at least twice as much food as is taken by a normal person of similar

sex, age, and height, continuously and until the goal is reached, after which the quantity may be gradually lessened. As the disease is alleviated by the gradual restoration of the metabolic balance, it is found that the enormous quantity of food required by (b) ceases to exist as a factor, and the patient progresses on much less an amount of food than before. Finally, the patient, having made a complete recovery, need take but a normal quantity of food to maintain his weight.

The Diet List.—Mere verbal instructions in the dietary régime and even brief, hastily written orders are practically useless. Nothing less than a carefully planned printed or typewritten diet list will suffice, indicating what to eat, how much to eat, how to eat, and when to eat. This discipline must be kept up with military rigidity, and no changes must be made by the patient or his household unless the doctor in charge is first consulted.

I have employed the following diet list for some years:

Diet List For.....
Date.....

GENERAL REMARK: DO NOT EAT FLESH FOODS

7 A. M.—*Breakfast:*

1. Fruit: Orange, grapefruit, stewed prunes, over-ripe bananas and cream, baked apples and cream, cantaloup, honey dew.
2. Cereal: Oatmeal, barley, rice, farina, "grape nuts," buckwheat cakes, hominy, mush.
3. Eggs: Soft boiled, poached, fried, scrambled, as desired. (Use no lard.)
4. Bread and Butter or Buttered Toast: As much as can be eaten.
5. Beverage: Milk (hot or cold), "Postum," chickory infusion, or hot chocolate.

Extra Nourishment: (10 A. M., 4 P. M., and 9:30 P. M.)

This may consist of one of the following:

- a. Two tumblersfuls of milk, hot or cold.
- b. Two tumblersfuls equal parts of milk and cream mixture (with a little vanilla and seltzer, if desired).
- c. Two raw or soft boiled eggs and a tumblerful of milk.
- d. Two or three raw eggs beaten thoroughly into the juice of one orange and a teaspoonful of sugar.
- e. Milk toast. (Several slices of bread or toast dipped into a bowlful of milk.)
- f. One tumblerful of cream (with vanilla, sugar, and seltzer, if desired).
- g. Fresh vanilla or chocolate ice cream, eaten slowly, with cookies or crackers, once daily.

1 P. M.—*Luncheon:*

1. Potatoes (baked, mashed, boiled, French fried without lard), or potato fritters.
2. Legumes: Small quantity peas, beans, lentils.

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3. Green vegetables: Cauliflower, spinach, lettuce, red tomatoes, squash, cucumbers, asparagus, carrots, onions, beets, corn on cob, egg plant, oyster plant.
4. Plenty of bread with butter or jam (made of figs, cherries, plums, blackberries).
5. Stewed fruit: Apples, peaches, pears, raisins, prunes, cherries, apricots.
6. Beverage: As at breakfast time.

7 P. M.—Dinner:

1. Soup: Vegetable, barley, rice, noodle, potato, corn (not canned), onion, bean (small quantity).
2. Eggs: In any form above mentioned.
3. Cheese: Cream or cottage cheese, with or without sweet cream or sour cream.
4. Fritters: Apple, banana, corn, potato, peach, squash.
5. Dessert: Puddings made of bread, apples, rice, tapioca, corn starch, chocolate, raisins, nuts, figs, dates; cup custards; small quantity bitter-sweet chocolates, chocolate peppermints, chocolate coated nuts.
6. Beverage: As at breakfast time.
(REMARK): Butter, crisco, and olive oil are the only fats permitted. Candy is never to be eaten between meals. Additional beverages such as buttermilk, kephyr, sour milk, and water may be taken throughout the day.

THE FOLLOWING SUBSTANCES ARE STRICTLY FORBIDDEN:

All flesh foods, meaning all things which must be killed.

All kinds of delicatessen and canned goods.

All spiced cheeses.

Hot breads, pastries and the like.

Under-ripe bananas and under-ripe fruits of all sorts, strawberries, water-melon, blackberries, huckleberries, gooseberries and raspberries.

Condiments of all sorts, especially pepper, horse radish, mustard, catsup, vinegar, sour pickles or tomatoes, and the like.

Beverages: Tea, coffee, cocoa, lemonade, alcoholic substances, an excess of carbonated beverages.

REMARKS: Avoid the extremes of temperature in food or drink. Eat slowly and chew your food thoroughly.

It will be observed that this diet list calls for three ample meals exactly six hours apart, with the choice of an extra nourishment about three hours after each meal. Feedings are so arranged that they are taken every three hours. Most patients will find it somewhat difficult to take the quantity of food required during the first week or two, but we soon find that a good, coöperative patient is capable of adhering to the list with rigid, clock-like discipline.

There are instances, however, in which the patient, despite an earnest desire to coöperate and abide by a strictly nonflesh dietary, simply cannot find the necessary level of contentment with regard to food, unless some concession approaching previously ingrained habits is made. Under these circumstances, the medical attendant may make an excep-

tion to the rule and permit a small portion of fowl,—chicken, duck, or squab, stewed or broiled, two or three times a week, and in occasional patients even daily. It is just this concession that may turn the tide in the quantitative aspect of the diet question and make for more rapid progress toward recovery. As the patient improves, this allowance of flesh food may either be continued or, better still, tapered off and finally withdrawn. Patients often claim that they could take very much more bread if permitted gravy in the diet. Here, too, an exception to the rule may help us toward our goal, for it is highly desirable that the patient consume a loaf or more of bread daily, and if gravy will assist the patient to take this quantity of bread, we must by all means permit it. The patient must be warned, however, that the gravy must not be too rich or highly spiced.

Miscellaneous Dietary Considerations.—There is a class of patients (and indeed of normal persons) who have an aversion to *bread*. The medical attendant should assert himself at the very start in insisting that this aversion must be overcome. Bread is truly the staff of life when the patient must gain weight, and unless a satisfactory allowance of it is taken, insurmountable obstacles will arise. Bread is usually taken with something else,—butter, perhaps cheese, milk, cream, or even jam. It is not difficult to conceive that when a patient takes plenty of bread daily the total food intake in caloric units is greatly increased, and the gain in weight is satisfactory. In many instances, patients who have apparently obeyed all instructions and still gain very tardily have been found to disobey instructions regarding bread allowance. When this is discovered, and corrected early, there follows a sudden rapid rise in weight and strength, and the alleviations of symptoms is surprising. I order my patient to consume a loaf of bread daily,—a loaf weighing 12 to 16 ounces. Though this seems excessive, it is really a moderate allowance. There are about 12 medium-sized slices to the loaf, and, distributing these evenly, it means the taking of 2 slices at each meal and each extra nourishment. Instead of the ordinary bread, toast or rolls may be taken in the same allowance. Whole wheat, graham or even rye bread may be permitted instead of the usual white bread, if desired. But the proper quantity must be insisted upon.

Often our patient asserts a craving for home-made *cookies* or *cake*. If these are baked with the permissible ingredients and are taken at least a day old, there is no objection to including them in the daily rations.

Milk and Eggs.—The most important constituents of the extra nourishments are milk and eggs, with occasionally cream, buttermilk, bread and butter, and other articles of food which may suggest themselves. Milk and eggs as extra nourishments are ideal, but many patients dread the idea of taking these foods, the aversion being more of men-

tal than of gastric origin. I have found that no matter how a patient dislikes milk or eggs, a method of preparation may be found to suit the palate, so that the objection is soon overcome and supplanted by a great liking for them. The best way to take milk is to sip it luke-warm, or to take it with a teaspoon. In this way it is partly digested in the mouth, becoming more tolerable to an irritable stomach. Milk which would create gastric discomfort, if taken in this fashion, may be imbibed in large quantities with impunity. If deemed feasible, a teaspoonful or less of milk of magnesia or a little sugar may be added. But if the patient's *mind* is made up against these foods, we must employ different tactics. How can we prepare milk to appeal to one who dislikes it? I would advise the reader to try the following preparations:

R Cracked ice $\frac{3}{4}$ ss
Granulated sugar 3 i
Essence of vanilla fl. dr. ss
Cold milk or milk and cream q.s. ad fl. oz. viii
Stir.

Seltzer, if squirted into milk a little sweetened, renders the latter acceptable to some palates. The seltzer must be ice cold and must not be used to excess,—just two or three short squirts to the tumblerful of milk. The following combination is relished by nearly everyone, sick or well, as it resembles in taste the usual ice cream soda procurable at the soda fountains:

R Cracked ice $\frac{3}{4}$ ss
Granulated sugar 3 i
Essence of vanilla fl. dr. ss
Pure cream fl. oz. i-ii
Cold milk fl. oz. iv
Seltzer q. s. ad fl. oz. viii
Stir and take through straw or tube.

At first one, then two, of these drinks are taken at a time. I have succeeded in inducing patients who formerly could not take milk to take three or four drinks of the above formulæ between meals. Moreover, it has often been seen that in many instances a person who passionately hates milk soon begins to like it and to look forward eagerly to the feeding hour.

Eggs may be taken in any form. The relative value of raw and boiled eggs has long been the subject of controversy. A few years ago, Bateman, as a result of experiments on animals, asserted that raw eggs may cause diarrhea with loss of some of the ingested material by the bowel. Later he cautioned against the use of large quantities of raw eggs in diet, insisting that they must undergo coagulation by heating before they can serve their purpose. Recently Rose and MacLeod have removed these objections, and as a result of experi-

ments on healthy persons at the Teachers' College at the Columbia University of New York, proved that the inclusion in a mixed dietary of a dozen raw eggs a day results in their satisfactory utilization, without discomfort, indigestion, or diarrhea. Every practitioner has seen his patients thrive on raw eggs as extra nourishment.

In the presence of a marked aversion to eggs, especially raw, I have succeeded in effecting a complete change of attitude by psychotherapy. Convince the patient that fresh eggs take the place of beef-steak but are devoid of poisons, and that a dislike for food is chiefly of mental origin, and persuade him to take the prescribed number of eggs as his share of the promised coöperative spirit, and the battle is won. Aversion to eggs and other foods is conquered in this way. Under such circumstances I have succeeded in persuading patients to take two or three raw eggs from the shell (with a pinch of salt) three times a day as "the appetizer" just before each meal. The matter of weight in such a patient ceases to be a serious question.

If desired, eggs may be soft boiled or poached, or beaten raw with milk or some other fluid. A milk-and-egg shake, consisting of a tumblerful of milk with an egg stirred into it, plus sugar and vanilla, is easily tolerated by most patients. Eggs may be beaten up in orangeade or lemonade; in fact, two or three eggs beaten into an orangeade may be administered to the patient, who will not even detect the presence of the eggs, especially if the drink is taken cold.

Many other methods of preparing milk and eggs may suggest themselves to the mind of the practitioner from time to time, for the purpose of enticing the patient to take extra feedings. It is advisable that when milk is taken, at least a pint of it should be consumed each time. If milk and eggs be taken, there should be at least two eggs and a tumblerful or two of milk. In lieu of milk and eggs, a tumblerful of cream may be taken, or two tumblerfuls of a half-milk-half-cream mixture. If buttermilk is desired, a pint or more of it may be taken instead of milk. The same may be said of koumiss and kephyr.

Cream is an excellent constituent of the dietary of these patients. Some are unable to digest it properly because of the excess of fat, so that it is necessary to mix it with an equal quantity of milk. In the course of a few weeks the patient becomes accustomed to undiluted cream which can finally be taken with impunity. Some patients can take a pint of it in divided portions each day; others much more. Cream may be employed not only as the liquid nourishment, but also in cereals, stewed fruit, and in other ways which may suggest themselves. I find that when the patient can take from a pint to a quart of cream daily in addition to a satisfactory allowance of other foods, the weight ceases to be a matter of concern, and the patient quickly obtains the normal, and even the 10 percent. excess for which we strive. In other words, when the patient's digestion is capable of tol-

erating pure cream, a status is reached wherein the digestive difficulties have been overcome. *Sour cream*, too, is an excellent element in the diet. Though quite as rich as cream, it does not cause digestive disturbances in the vast majority of instances, and because of its contained lactic acid bacilli, serves also as an aid in overcoming intestinal disturbances. Sour cream may be mixed with cottage or cream cheese or even with boiled potatoes, or taken with bread, crackers, or home-made cookies.

About three years ago McCarrison, experimenting on pigeons, pointed out that the addition of *onions* to a dietary rich in protein and fats markedly retards the development of thyroid hyperplasia and the tendency to acinar budding. The beneficial influence of the onions is held to be due, in part at least, to their action in restraining the growth of putrefactive types of bacteria in the gastro-intestinal tract and in retarding the absorption of their products. This observation seems to confirm my views of onions as an asset in the dietary of the subject of Graves' disease. I have been suggesting the use of a small raw onion each day to these patients since 1909, and have recently included onion soup in the dietary. Onions seem to agree perfectly with these patients, and on theoretic grounds, at least, possess distinct therapeutic virtues.

Cod Liver Oil is a food and a valuable therapeutic agent in this affection, but can be supplanted successfully by cream and olive oil. The iodin in cod liver oil is a valuable asset to the medicinal treatment of many patients, but iodin in other forms serves just as well. Cod liver oil is difficult for most people to take, and we find in most instances of Graves' disease that the delicate digestion prohibits its use, rendering the taking of substantial food more difficult. So that, despite its inherent value, I rarely, if ever, employ cod liver oil in this disease.

Olive Oil is very useful in Graves' disease, as a therapeutic agent, as a food, and as an adjuvant in the preparation of other foods. Following a preliminary distaste for it in the majority of patients, olive oil is soon tolerated and can eventually be taken with ease in doses of one to four ounces at a time. Not possessing the disagreeable taste of cod liver oil, patients find it easy to just "slip it down," two or three times a day at the time corresponding to the taking of the extra nourishment. Incidentally, olive oil is an excellent substance for frying, but crisco or butter may likewise be used for this purpose.

Diet and Diminished Carbohydrate Tolerance.—Despite the fact that in exophthalmic goiter there is diminished carbohydrate tolerance, as evidenced by hyperglycemia and glycosuria, there are no definite changes in the islands of Langerhans, thus differentiating the clinical situation from that of diabetes mellitus. It has been my practice to disregard completely the matter of carbohydrate intolerance in Graves'

disease in the making up of the diet for these patients. There must be no curtailment of starches or fats, for it is upon these elements that we depend largely for the restoration of the patient's health and strength. Indeed, and strange as it may seem, subsequent events show that the patient, despite blood and urinary evidences of intolerance, has an undue tolerance to starches and fats, for, as improvement becomes evident through the use of these foods and recovery is reached, glycosuria and hyperglycemia disappear. Of course, Graves' disease and a frank diabetes mellitus may exist in the same patient, but this is the exception to the rule, and a subject of this sort must be managed somewhat differently. The remarks herein contained apply only to uncomplicated cases. However, given a patient in whom Graves' disease plays apparently a more devitalizing rôle than the complicating diabetes, the consideration of the latter disease must be subordinated to the management of the former, and the patient treated in accordance with the principles herein described, until marked improvement is observed in the Graves' syndrome.

Forced feeding, with mental and physical rest and other elements in the treatment of Graves' disease, is also ideal in an associated tuberculosis as mentioned in another chapter.

The Appetite.—When asked concerning the appetite, the average subject of Graves' disease usually responds: "My appetite is fine. I eat all day, but I don't know what becomes of the food, as I am losing weight constantly." These patients may complain of wasting, nausea, vomiting, diarrhea, and hyperhidrosis, but the appetite may be sharp, even ravenous. Yet it is the wasting, nausea, vomiting, diarrhea, and hyperhidrosis, which bring about a hunger of the body, asserting itself in a good appetite. However, the desire for food varies and the appetite, though good and sharp, is usually quickly satisfied, unsustained and capricious. Thus, after the first few mouthfuls the patient may find himself satiated and stop eating, only to feel hungry an hour or two later. In a percentage of patients periods of hunger alternate with periods of anorexia, the appetite, and indeed the digestion, waxing and waning with the vacillation of the emotional status.

The quickly satisfied appetite is one of the most difficult problems in the quantitative aspect of the diet. The patient finds it difficult to continue eating beyond a mere fraction of the prescribed quantity of food. On being urged to eat more, the usual response is: "Doctor, I eat all I can. When I feel I've had enough, I must stop, because I may vomit." The doctor must take this attitude tactfully in hand with the following argument: "Don't mind the vomiting. Obey orders, even if you vomit each time. The time will come when you will forget to vomit, and then you will enjoy taking enormous quantities of food. Unless you virtually eat your way to recovery, your difficulties are multiplied and you may not get well. You have been in the habit

of under-eating. You must acquire the habit of over-eating, even if it hurts. Your sense of being satisfied after eating is an unreliable and dangerous guide. Your desires, likes, and dislikes, must not be consulted until such time as you are discharged cured. Just as you must quench a fire with an excess of water, so must you quench the fire of this disease with an excess of food. To employ just enough water during a conflagration means a smouldering of the fire, with an outburst of flames later on; to eat just enough will mean mere improvement, with a rekindling of slumbering fires into the flames of a relapse. You must overwhelm, oversaturate your tissues with great quantities of food, so to extinguish the flames within you as to leave no doubt of the permanency of results. It is only by eating the prescribed quality and quantity of food that you will regain your lost weight and obtain a slight excess in weight,—the essential requirement toward health and happiness. The task is difficult, perhaps a torture, but it is a matter of several months only. Is it not better to endure the temporary torture of forced feeding, with recovery in sight, than the perpetual torture of the disease with its inevitable consequences?" No patient still sane can resist the argument, and coöperation is had without further difficulty.

Monotony in Diet is frequently encountered even though the dietary list herein contained, if carefully studied, is really very liberal. If such an attitude is reached, the patient must again be taken to task, and must be informed kindly but firmly that the digestive organs do not understand monotony; that this is an attitude of the mind only; that the food is to be regarded as a medicine, if necessary, and as such must be taken in the proper doses, irrespective of aversion, and that in course of time the pleasure of being a well person will more than compensate for the discomfort endured during the course of treatment. Monotony may be overcome by sundry changes in the preparation of food. Eggs may be prepared in a dozen or more ways, each constituting a *variety* as far as the eye and taste are concerned. The same may be said of potatoes, noodles, cheese, fruit, and even milk. Variety may be a stomach factor, but it is even more a psychic factor, and if the egg or potato or cheese is prepared in a different way than ever before and the taste partially disguised, and the dish is made good to look upon and of unusual palatability, we are giving the patient a new dish and increasing his food intake.

Digestive Disturbances.—In the presence of symptoms of digestive disorders,—such troublesome factors as nausea, persistent vomiting, pyrosis, diarrhea, abdominal discomfort, and the like, constituting a major obstacle to improvement, what are we to do? The question of *avoirdupois* must wait upon improved digestion and a correction of the symptoms mentioned, as the food administered may act as an irritant rather than a restoring agent. Nervous indigestion is the most

common difficulty, a functional condition participating in the symptom-complex presented by the patient and largely due to the peculiar nervous makeup characterizing the Basedowian subject. Of course, it is recognized that since these digestive disorders are of nervous origin, they should improve on the amelioration of the cause. But the continued digestive disturbances, a *result* of the nervous status, have also become a *cause* of it, and unless we break this vicious circle by attention not only to the nervous system, but also to the digestive organs directly, so that more food is tolerated, we will fail in our purpose.

Though it has often been said that hydrochloric acid is sometimes diminished or absent in exophthalmic goiter, this is rarely the case. In almost every instance there is an excess of acid which, if overcome, is a relief to the patient. In cases of this sort the administration of milk of magnesia, 2 to 4 drachms an hour or two after meals, is of service. This will also overcome any existing constipation. If the bowels are still infrequent and fecal retention is suspected, a teaspoonful of sodium phosphate in a tumblerful of warm water taken an hour before breakfast every day is advised. If diarrhea prevails, we must combine the magnesia with a bismuth salt. I have found the following prescriptions of use in these cases:

Formula 1: Rx Bismuth Subcarb. gr. x
Magnes. Oxid. Ponderos. gr. vi
Ext. Hyoscyamus gr. $\frac{1}{2}$
M. et fiat chart. No. 1. Mitte No. XX.
Sig.: One powder t. i. d. an hour after meals.

Or Rx Bismuth Subcarb. gr. viii

Formula 2: Rx Pulv. Ext. Rhei gr. ii
Ext. Hyoscyamus gr. $\frac{1}{2}$
M. et fiat caps. No. 1. Mitte No. XX.
Sig.: 1 capsule an hour after meals.

In cases where nausea and gastric discomfort are prominent, the following will be found highly useful:

Formula 3: Rx Codein Sulph. gr. iv
Tr. Hyoscyamus fl. dr. vi
Bismuth Subcarb.
Magnes. Oxid. Ponderos. a.a. 3 iii
Essence Pepsini q.s. ad fl. oz. vi
Misce.
Sig.: Shake well and take a teaspoonful in water a half hour before and after meals.

In the above formula the bismuth and the magnesia may be increased, diminished, or one of them omitted, depending upon the degree of gastric discomfort and the presence of diarrhea or constipation, as the case may be. The codein in this formula will to an extent allay the irritability of the nervous system, but since one might object to it

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because of its habit-forming quality, we must give it for a short time only, or perhaps substitute the following:

Formula 4: Rx Veronal

Pulv. Ext. Rhei a.a. gr. ii

Bismuth Subcarb.

Magnes. Oxid. Ponderos. a.a. gr. viii

Ext. Hyoscyamus gr. $\frac{1}{3}$

M. et fiat chart. No. 1. Mitte XX.

Sig.: 1 powder one-half to one hour after meals.

Or Rx Luminal-sodium gr. iv

Formula 5: Rx Sodii Bicarb. 3 iv

Ess. Menth. pip. fl. dr. iii

Aquaæ Cinnamomi q.s. ad fl. oz. iii

Misce.

Sig.: Teaspoonful one-half hour after meals.

Or Rx Sodii Bicarb. 3 iv

Formula 6: Rx Tr. Opii Camph. fl. dr. vi

Tr. Hydrastis

Essence Menth. pip. a.a. fl. dr. iii

Aquaæ Cinnamomi q.s. ad fl. oz. iii

Misce

Sig.: Teaspoonful after meals.

In the presence of persistent diarrhea, rectal injections of adrenalin chloride solution may be employed, as mentioned in the chapter on Medicinal Treatment. The following is also very efficient:

Formula 7: Rx "Tannigen"

Bismuth Subnitrate a.a. gr. vii

M. et fiat chart. 1. Mitte XX.

Sig.: 1 powder 3 or 4 times a day until relieved.

The ingredients may be varied in dosage according to therapeutic indications. I cannot recommend these veronal- and luminal-containing prescriptions too highly, as they are the most efficient formulæ I have employed in the gastro-intestinal disturbances accompanying exophthalmic goiter. In extreme retching and vomiting, cocaine hydrochlorate gr. $\frac{1}{4}$, alone or combined with any of the above formulæ, administered for a short period, will yield prompt results. The patient can now retain food and enjoy it. There is an increase in appetite, the weight improves rapidly, the nervous symptoms are gradually quieted, and sleep becomes refreshing. Of course, a relapse in the digestive symptoms is always a possibility, especially when something has occurred to excite the patient in some way. This must not discourage us, however, for, as a rule, an extra dose or two of the above formulæ or similar combinations and an effort to dispel the cause will usually overcome the difficulty, and the patient is again on the road to recovery.

Psychic Factor in Feeding.—Nausea, vomiting, and miscellaneous

symptoms of indigestion are the main obstacles to forced feeding in Graves' disease. Medication is capable of overcoming some of the difficulty, but more than that, psychotherapy serves a distinct purpose in this regard. The patient must be convinced that the dietary treatment can and must be carried out, and an effort at persuading him to coöperate in a prompt, whole-hearted way at the very start is vital.

There is such a thing as a diminished stomach capacity or habitual undernutrition in which the organ has acquired the habit of holding much less than the body requires. This gives rise to deficient digestive functions, and the patient, experiencing discomfort after eating, denies himself further food to overcome discomfort. In course of time this circle becomes so vicious that the food intake is hardly sufficient for the maintenance of life. Weakness, anaemia, and other physical and mental disturbances complete the picture frequently seen in patients in whom undernutrition is the actual cause. Properly applied psychotherapy can cope successfully with the situation.

Deficient enthusiasm, diminishing morale, a beginning carelessness and evidences of equivocation in discipline in a patient with Graves' disease must be nipped in the bud by careful vigilance of the internist, for if these become a habit, the patient may slide back to his original slip-shod mode of existence, and all is lost. Success or failure depends upon military discipline in obedience to instructions. The patient's daily habits and conduct must be completely dominated over by the understanding, individualizing internist. If there is anything like a secret in the successful nonsurgical management of Graves' disease, it is this: *The control of the patient must be unequivocal and complete until the goal is reached.*

Place the subject of Graves' disease in pleasant surroundings; keep him in bed sixteen hours a day; administer a well-calculated régime of superalimentation; continue this régime of tranquillity, rest and feeding for several months, and the patient will recover. Pleasant surroundings alone are futile; rest alone is futile; forced feeding alone is an impossible procedure and futile. Drugs and other measures are at best supplementary. It is the happy combination of *peaceful surroundings, physical and mental repose, forced feeding, and careful medication*, upon which the patient's future health and usefulness depend.

Weight and Progress.—The very best sign in the world that our treatment is just right is a material improvement in weight, and this, as already intimated, cannot be accomplished without dietary considerations. No matter what we do for the patient,—no matter how careful, how skillful we may be in therapeutics, if the weight is at a standstill or only slightly improved after a few weeks' trial, the struggle will be a difficult one, to say the least. On the other hand, we might say that *all means of endeavor should have as a prime object a rapid restoration of the standard weight of the individual*. If we succeed

in this, the treatment succeeds, and the patient recovers. A gain of 5 pounds during the first 2 weeks, let us say, is almost always associated with a reduction of the heart's rate by at least 10 beats per minute; the subjective cardiac distress is reduced; the expression becomes less anxious and more hopeful; the entire demeanor is one of renewed confidence in the future. The patient looks forward to meal times, sleeps better, arises in the morning less fatigued and more refreshed, and in general everybody sees a change for the better. Thus we have accomplished the first definite step toward victory, and the patient bids fair to make uninterrupted progress until completely well,—restored to happiness, usefulness, and longevity. A patient who responds promptly to a properly outlined régime should gain an average of $2\frac{1}{2}$ pounds a week during the first month, after which time an average of $1\frac{1}{2}$ or 2 pounds a week can be expected for several weeks until the weight is restored to the normal figure. It usually requires from 12 to 20 weeks to regain the former standard of weight. The increase is at first rapid, becoming much slower as the normal figure is approached. Occasionally, a patient may gain at the rate of 4 or 5 pounds a week during the first 3 or 4 weeks, then remain at a standstill for a week or two, after which an increase of a pound or two a week continues until the normal figure is reached. Most often the weight continues to increase to above the normal figure, and it is not uncommon to find that the discharged patient weighs 10 to 20 pounds more than ever before. It has been my practice to safeguard the patient's interests by insisting on an increase of 10 percent over and above the normal standard of weight, as a requirement to discharge from treatment. The internist who has succeeded in effecting this increase during treatment of a subject suffering with Graves' disease has succeeded in effecting a restoration to normal of the basal metabolism and the pulse rate. A slight *surplus* weight and normal basal metabolism and pulse rate are synonymous with recovery from Graves' disease, for by this time such signs as exophthalmos, goiter and other evidences of the disease have either left the patient or are rapidly disappearing.

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CHAPTER XXIII

LOCAL MEASURES IN THE TREATMENT OF EXOPHTHALMIC GOITER

LOCAL measures intended for a direct effect upon the thyroid gland are usually unnecessary in the broad management of subjects of Graves' disease. However, when the thyroid swelling seems to be excessive, and the organ appears unduly vascular, certain local measures may supplement general treatment. These measures may be divided into: (1) Thermal; (2) mechanical; (3) medicinal; (4) x-ray; (5) radium; and (6) miscellaneous forms of electricity; (7) injection treatment.

1. THERMAL LOCAL MEASURES

Heat is never to be employed over the thyroid gland, as the organ, already congested, tolerates it badly. *Cold* in the form of the Leiter coil, or, better still, an ice bag, is highly serviceable. Cold reduces subjective throbbing, and in its effect is as grateful to the patient as an ice bag applied over the turbulent heart. Indeed, two ice caps should be used in very sick patients,—one over the thyroid and the other over the precordium. The ice bag over the thyroid should be so filled and applied as to fit snugly and comfortably about the organ, and so fixed that it does not move away from its position with slight change of posture of the patient. Again, the cold should not be applied to the point of pain. When the patient begins to complain of pain from freezing of the skin, the ice bag is removed and reapplied an hour later, again to be removed when the point of discomfort is reached. Thus the bag may be employed during 6 or 8 of the waking hours, a period of time sufficient to accomplish its purpose. In the course of a week or two, other measures employed will have improved the patient sufficiently to render the ice bag unnecessary.

2. MECHANICAL LOCAL MEASURES

Adhesive plaster, *flexible collodian*, and the like, placed about the thyroid, as advocated years ago, are incapable of any good in these patients.

The *goiter binder*, mentioned under treatment of simple non-surgical goiter, may be employed with advantage. Mild pressure upon the vascular, hyperplastic thyroid, during the institution of other more

general measures, serves to encourage the organ to a more prompt restoration to normal vascularity and vesicular structure. The binder should be properly applied. The patient should feel its presence and moderate persistent pressure, but not pressure enough to produce discomfort or interfere with sleep. It need not be worn during the waking hours.

3. MEDICINAL LOCAL MEASURES

The tincture of iodin, lauded years ago, should not be employed, not because of the iodin contra-indication, but because of the irritation which, after the second or third application, causes the skin to become parchment-like and inflamed. Moreover, the discomfort and pain, the discoloration of the skin and consequent embarrassment, and the possibility of a troublesome eczema, are apt to increase the nervousness of the patient. The so-called colorless tincture of iodin does not discolor the skin, nor does it possess any therapeutic virtues. If iodin is desired locally, a weak iodin solution or a nonirritating ointment containing iodin or one of its salts may be employed.

Formulae for application over the thyroid area have been suggested in the chapter on treatment of simple physiological goiter. These may be employed in hyperplastic goiter as well. The following additional formula is suggested:

R Ungt. Hydrarg. Oxidi Rubri 3 1/4
Ungt. Potassii Iodidi q.s. ʒ ii
Misce.

A small portion, the size of a lima bean, is to be rubbed over the goiter area until absorbed, after which a small quantity is to be lightly smeared over the thyroid area, and a piece of flannel placed about the neck and kept on all night. The goiter binder may then be applied over the cloth.

4. X-RAY TREATMENTS

Whether or not the roentgenologist is aware of it, he belongs, in common with the surgeon, to that school of therapy of Graves' disease which believes that hyperthyroidism is the cause of the affection and that a destruction of a variable portion of thyroid structure is the rational therapeutic approach.

The treatment of Graves' disease by the x-rays presents an interesting chapter in the controversy on the treatment of exophthalmic goiter. Enthusiastic, I should say radical, roentgenologists claim their form of treatment as superior to all other measures; the more conservative observers, especially in recent years, while still claiming cure in a large percentage of cases, admit many failures, and give credit

to other forms of therapy as being of distinct service in this disease.

The action of x-rays is based on the property of glandular inhibition, observed when living tissue is exposed to the rays. Small doses are stimulating and large doses inhibitory in their effects, while very large doses cause atrophy. Following inhibition of function, the continuation of effects leads to cellular alteration, with final necrosis, to such an extent that occasionally a case of Graves' disease is converted into one of myxedema. On the contrary, an instance is occasionally met with in which an increased glandular stimulation was the result, with intensification of the symptoms. Let us examine the opinions of clinicians on this subject, gleaned from the literature.

Among the first who called attention to x-ray treatments of the thyroid are Beck in 1900, Williams in 1902, Pusey in 1903, Stegman and Görl in 1905, Mayo and Freund in 1907, Pfahler in 1908, and Pfahler and Zulick in 1916. The subsequent bibliography is rather comprehensive. Such names as Secher, Florence Stoney, Seymour, Holmes, Schlecht, Allison, Bear and McKinley, Fischer, and Crile figure largely in discussion on the roentgen therapy of exophthalmic goiter.

Of the 80 cases under treatment at the Massachusetts General Hospital, Seymour reports all improved except 7. Five of these showed no change, and 8 were completely cured of their symptoms.

Pfahler and Zulick believe that the x-ray has a field of distinct usefulness in the treatment of this form of goiter. They believe that preliminary roentgenogram of the chest should be made in all cases in order to obtain some information as to thymic size and as to substernal extension of the goiter. When the thymus is not found enlarged, a single dose directed through the sternum will be sufficient. When it is enlarged, the rays should be passed through two fields on either side of the median line below the clavicles, including the first, second and third spaces. Regarding the dosage of x-ray treatment, Pfahler says: "Generally speaking, with a Coolidge tube, transformer current, a parallel spark gap of 9 inches, and the target of the tube 8 inches from the skin, 5 milliamperes of current given for five minutes through 3 mm. of aluminum and one layer of sole leather, will give 18 to 20-x or approximately double tint "B," and this is the dose we generally give."

Florence Stoney, in a series of 48 cases of Graves' disease treated with x-ray, reports 14 cures, 22 cases sufficiently improved to return to the duties of life, 4 who were unimproved, 7 who discontinued treatment too soon to form an opinion regarding the efficacy of the treatment, and 1 in whom the pulse rate fell from 136 to 112 and who died twelve hours after operation. She gave 6 milliamperes 5 minutes at a focal distance of 6 inches, treating each lobe separately. Treatments were given twice a week for a month; at times a slight dermatitis was produced. An interval of two weeks was allowed between a month's series

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of treatments, and the total length of time of treatment was from six to eight months.

Secher reiterates that the enlarged thyroid gland responds to roentgen treatment in very different ways in different cases. In several cases cited, an ordinary goiter seemed to become transformed into the exophthalmic type under roentgen treatment. That the roentgen rays are free from danger is not true. The thyroid may be whipped up to excess function, or it may become functionally insufficient. A tendency to myxedema, however, is rare, but numerous cases of aggravation of hyperthyroidism have been reported, even with the most modern improved technic. Rieder and Verner have each reported 1 or 2 cases in which the aggravation was so intense that the patient died, and Secher now adds another case to this list of fatalities. His patient was an unmarried woman of forty, previously healthy until exophthalmic goiter developed. The thyroid was given roentgen treatment after a year, eight exposures, each $\frac{1}{2}$ Saubouraud Noiré unit distributed in four fields, three on the thyroid and one on the thymus. Her symptoms became much aggravated at once, with restlessness, choreiform movements, pulse 100 to 200, and heart beat up to 240, respiration 72, and death on the fifth day. The thyroid showed very slight changes and the thymus nothing abnormal.

Holmes and Merrill state that the dangers incident to roentgen treatment are that the functions of the thyroid may be destroyed, with resulting hypothyroidism; telangiectasis may occur, and even the first treatment may increase toxemia to a dangerous degree.

Cordua reports the case of a woman of 38 who showed all the classical symptoms of Graves' disease, and in whom x-ray treatment resulted in typical myxedema.

Béclère claims that radiotherapy is the ideal treatment for Basedow's disease and for all forms of hyperthyroidism, for it destroys the secreting elements, or, at any rate, diminishes their secretory activity. When the morbid condition does not date back more than a year and the gland is soft, treatment by intensive doses at long intervals takes only from two to three months. In chronic forms, with a hard gland to which are added hyperplastic lesions of the connective tissue, the treatment takes at least six months, and improvement remains incomplete. In simple hyperthyroidism, on the contrary, radiotherapy is always perfectly successful, but it is in serious forms with extreme wasting and intense rapidity of heart action that this method gives the best results. Irradiation should be penetrating (20 cm. equivalent spark gap, 5 mm. aluminum, 20 cm. distance from the anticathode, localizing cylinder 10 cm. in diameter), seances should be weekly, and the dose 3 H.

Fleischner, of the First Medical Clinic in Vienna, reports a case of Graves' disease in a woman aged 41, with a cutaneous edema of the lower part of the body resembling scleroderma, in whom irradiation of

the ovaries was followed by amenorrhea and aggravation of the general condition. He alludes to two other cases on record in which x-ray treatment had a similar effect.

Belot, the *chef de laboratoire* at the Saint-Louis Hospital, reports partial improvement in 20 percent. of forty-five cases of exophthalmic goiter given roentgen-ray treatment; 70 percent. with definite and prolonged improvement, and no benefit in 5 percent. of those who completed the course. He declares that this treatment begun in time gives surprising results; it is more promptly effectual in the acute forms.

Trier, between 1913 and 1920, has treated about 200 cases of Graves' disease at the roentgen department of the Rigs Hospital in Copenhagen. In the course of two months he has personally examined 88 of these patients, and he has received reports on several others. A comparison of the results showed that there was little to choose between giving (1) small exposures over a considerable period; (2) small exposures over a considerable period, the thymus being included; and (3) big exposures, both the thyroid and thymus areas being included. Trier's opinion of the value of x-ray treatment is guarded; it may be an excellent supplement to general medical treatment, giving this in many cases just the support needed to tip the scales in the patient's favor. But it is not of epoch-making importance, and it seems to matter little whether the thymus is treated or not.

Mayo (*Medical Record*, June 18, 1921) saw two cases of carcinoma of the neck due to x-ray treatment of goiter.

Allison, Beard, and McKinley, in an exhaustive study of the x-ray treatment of toxic goiter, give the following data and conclusions: Of the 27 cases of Graves' disease without complications who were subjected to x-ray treatment but were not operated upon, 24 are well, both from the clinical and laboratory standpoint. The treatment has been complete for nearly eight months. The remaining three cases came to operation. Of these three, one was definitely improved before operation, and the other two were normal a few months after operation. Of 6 cases of postoperative hyperthyroidism which had relapsed, one showed a definite cure. The other 5 showed no improvement. Of 3 cases of thyrotoxic adenoma none showed any responses to x-ray therapy. The only subject of the series who was operated upon during an increasing basal metabolic rate died an operative death. The results obtained in the earlier cases might have been attained more quickly if more intensive therapy had been used. No bad results or complications which could be attributed to the treatment occurred in any of the series. Their experience with this treatment was convincing that only with the closest possible coöperation between the clinician and the roentgen therapist can satisfactory results be obtained.

Haudek and Kriser, of the Vienna roentgen laboratory in charge of Holzknecht, discuss the practical results of roentgenotherapy in the

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treatment of exophthalmic goiter. Their observations cover 38 cases, in 12 of which the patients have been reexamined; 4 of these can be regarded as cured; 7 are much improved, and 1 is slightly improved.

The conclusions of Means and Holmes, in a recent paper on the subject, are interesting and valuable: "We believe that . . . the roentgen ray probably has a beneficial effect in toxic goiters, and for this reason it has its place in our armamentarium for treating these diseases.

"About two-third of the patients with exophthalmic goiter so treated show either recovery or improvement with the treatment. The remaining third neither improve nor grow worse.

". . . Prolonged roentgen-ray treatment in patients showing no response is undesirable. This is a fact which has been impressed on us particularly in our recent work. We have not emphasized it before, and therefore do so now.

"In toxic adenoma there seems to be a similar improvement to that noted in exophthalmic goiter, but so far we have used it only with patients who have refused operation. In toxic adenoma, in contrast to exophthalmic goiter, surgery probably removes the actual cause of the disease, the adenoma. The indication for surgery would, therefore, seem more definite than in exophthalmic goiter. Even in toxic adenoma, however, in certain cases that are too thyrotoxic for safe operation, the roentgen ray may be used to advantage.

"To make a proper use of the roentgen ray in the management of toxic goiter of either variety, its limitations should be recognized and it should be intelligently correlated with other therapeutic measures as the individual case may demand."

These observers advise the following technic: An exposure at 8 inch target distance using a Coolidge tube energized with a rectified current of a voltage capable of breaking an 8-inch air gap between blunt points. The rays are filtered through 4 mm. of aluminum and one thickness of sole leather. The exposure time and the number of milliamperes passing through the tube are varied somewhat, but their product has been kept fairly constant, from 35 to 40 milliampere minutes being the usual exposure. They often increase the target skin distance to 10, 12, or even 16 inches: these increased distances, of course, require a corresponding increase in time of exposure. Three areas are exposed; one on each side of the neck over the thyroid, and one over the upper part of the sternum over the region of the thymus. The size of the areas exposed is usually a square of about 3 inch diameter. Treatments are given at about 3 week intervals.

Comparative Claims of Surgeons and Roentgenologists.—Many articles appear from time to time in which surgeons on the one hand and roentgenologists on the other claim greatest merit for their respective procedures in the treatment of Graves' disease. Among other things surgeons claim that

1. X-ray treatment does not yield results sufficiently often and in sufficient degree to warrant its use in preference to surgery;

2. X-ray treatment is incapable of precise dosage, and is therefore uncertain in results;

3. X-ray treatment frequently results in myxedema;

4. X-ray treatment frequently results in acute exacerbations of hyperthyroidism;

5. X-ray treatment is occasionally the cause of sudden death;

6. X-ray treatment often results in such accidents as burns, keloid, cancer of the neck, atrophy of the skin, and telangiectasis;

7. X-ray treatment renders surgery more difficult because of adhesions occurring within the goiter through irradiation;

8. X-ray treatment, when relief is obtained, yields benefit too slowly.

On the other hand, roentgenologists argue that their method of treatment is superior to surgery for the following reasons:

1. X-ray treatment is bloodless;

2. X-ray treatment is painless and devoid of inconvenience to the patient;

3. X-ray treatment does not interfere with the patient's occupation;

4. X-ray treatment is not associated with shock;

5. X-ray treatment does not cause scars;

6. X-ray treatment is devoid of a mortality rate;

7. X-ray treatment is not associated with the accidents to which surgery is susceptible;

8. X-ray treatment yields a larger percentage of good results than surgery.

Crile, Richardson, and others have been among the most recent observers to make comparisons between the end results of surgery and of x-ray treatment. Depending upon whether it is the surgeon or the roentgenologist who makes the comparison is the weight of favorable opinion the greatest on the one side or the other.

It is not with the respective methods of procedure that the internist contends. The argument that concerns us is the question of *rationale*, i.e., whether Graves' disease is due to hyperthyroidism and therefore whether a destruction of thyroid structure and function is the proper procedure. The most experienced roentgenologists happen to be the most conservative when discussing the question. According to the majority of these observers, roentgen therapy is very useful in early cases; it is of service in moderately advanced and in advanced cases, but except in early cases, this form of treatment is merely of supplementary value, rarely, if ever, the mainstay. The eyes and thyroid are not often benefited; the patient is merely improved, not cured, and is therefore still an invalid, unless something broader and more substantial is done to overcome the numerous vicious circles characterizing the disease.

Personally, I employ x-ray treatments in a very small percentage of cases *as a supplement to other more widely distributed measures* in the broad management of Graves' disease. Believing that thyroid hyperplasia is not the cause but an ally, a defensive reaction, a natural attempt to protect the individual against poisons originating elsewhere in the body, the thyroid, *per se*, requires little if any attention. But it must be admitted that in a small percentage, perhaps 5 percent. of cases, the thyroid, so to speak, runs away with itself from overcompensation, and when this happens, supplementary x-ray treatment may be of service. In my experience, x-ray treatment alone is futile; as a supplement in the class of cases just described recovery is hastened.

5. RADIUM

During recent years radium is occupying an increasingly important place in the therapy of hyperplastic goiter. Aikens reports several cases of exophthalmic goiter in which radium, combined with approved non-surgical measures, yielded satisfactory results. He has treated 45 such cases with radium. He states that of these, 23 have been clinically cured; that is, the tachycardia, tremor, and restlessness have disappeared, and symptoms of excessive thyroid secretion have abated. In 17 cases there has been an improvement. The characteristic point in connection with the treatment was the relief of the nervous symptoms. In only a few of the cases did the gland diminish in size.

Turner has treated to date upwards of 50 cases of exophthalmic goiter with radium, and, with one exception, all have been in some degree benefited. The exception was a woman of 22, who died within two weeks after the treatment of "toxic thyroidism." The benefit that patients with exophthalmic goiter derive from the expert application of radium is in their general symptoms. They regain strength and weight, and the tachycardia and breathlessness diminish or disappear. The thyroid gland becomes harder, but usually not smaller, a fact of which it is wise to forewarn the patient to prevent disappointment. Exophthalmos is little effected. Turner treats each lobe and the isthmus of the thyroid, and the thymus. A dose of 200-300 milligram hours, with proper screening, is given over each area, and the patient sent home for three months. Then, if necessary, the treatment may be repeated. The skin in the throat region is very sensitive to the rays and must be carefully protected. Turner claims that as compared with x-rays, radium permits more exact dosage, penetrates better and is not disturbing to a nervous patient.

Mowers is more enthusiastic over the use of radium, stating that the majority of the cases of exophthalmic goiter are clinically cured thereby and a very large percentage have an actual decrease in the size of the goiter.

Loucks claims that radium is the treatment of choice because it is portable, less exciting, easily controlled, does not produce sudden toxemia, and the results are more promising than with x-rays. Radium treatment must be supplemented with the usual medicinal treatment. He employs at least 100 mgm. of radium in four tubes, each tube screened in 1 mm. of brass and 1 mm. of gum rubber. The screened tubes are placed on a gauze pad 2 cm. thick to get distance and protect the skin. Two or more ports are exposed over the thyroid, depending upon the size of the gland, size of the pad, and the amount of radium used. The time of exposure is from eight to ten hours over each port.

Terry in 1921 and in 1922, reports on the use of radium emanations in the treatment of "bad risk cases" of exophthalmic goiter, which consists of the introduction into the hyperplastic thyroid of the bare tubes containing the emanations.

Further knowledge of radium and experience in its application in the management of subjects of Graves' disease is obviously essential ere we can make definite statements regarding its efficacy in this affection.

6. MISCELLANEOUS FORMS OF ELECTROTHERAPY

Galvanism is of service in many instances, and has the advantage of being devoid of discomfort. Schvostek (quoted by Möbius) employs this current as follows : (1) To the sympathetic nerve: anode to sternal notch, cathode to the angle of the jaw for one minute; (2) to the spinal cord: anode over fifth dorsal vertebra, cathode on the neck; (3) through both mastoid processes: weak currents and daily sittings. Foubert employs galvanization with electrodes on the abdomen and thyroid. He remarks that the treatment has no contra-indications and is absolutely without danger; the thyroid can stand a much stronger current without disagreeable symptoms than other parts of the body. I find galvanism of distinct service, and give 10 milliamperes as mentioned under physiological goiters. Solis-Cohen occasionally modifies galvanism by the sinusoidal apparatus (60 to 90 interruptions per minute) placed over the side of the seventh cervical vertebra.

The High Frequency Current applied with the glass vacuum electrode has been of service in a few of my cases. The electrode is applied over the thyroid gland, ten minutes at a sitting, two or three times a week. I have observed that this current, weakly applied over both eyes by means of a binocular electrode, has been of marked service in rapidly ameliorating several cases of extreme exophthalmos.

Faradism has been tried with varying degrees of success. Hase reports good results from the use of the faradic current applied over the thyroid in a series of mild and moderately advanced cases of Graves' disease; there was no improvement in his serious cases.

The Electric Bath and various miscellaneous forms of electricity have been employed by observers with reports of success which was probably due to suggestion.

D'Arsonval Current (Autocondensation) administered in the chair or couch is an efficient method of mental suggestion, and seems also to possess genuine alterative or tonic properties. Two hundred or more milliamperes are given according to indications. In most patients the vasomotor instability is overcome, the glycosuria is diminished, the nervous irritability reduced and the tachycardia relieved. Of course, the effects of this treatment last but several hours, but the superimposition of effects may be accomplished by daily sittings of 15 to 20 minutes, which method is very satisfactory, assisting the patient to a state of well-established improvement. This treatment is of greatest service in instances of hypertension and also where it is believed there is an admixture of hypo- with hyperthyroidism. It should not be employed in patients with hypotension and hyperidrosis, as this treatment reduces blood pressure and increases sweating.

Iodin Cataphoresis has been employed by some observers, but this mode of treatment is of doubtful value in subjects of Graves' disease.

Static Electricity, especially in the nature of the static wave current, is highly useful in the local treatment of the hyperplastic thyroid, as suggested in 1908 by Snow, who pointed out that "Energetic successive contraction and relaxation, with a not too rapid discharge at the spark-gap, induces an active tissue gymnastics throughout the substance of the gland, thereby forcing out all infiltration and removing inflammatory products, and thus restoring the normal metabolism. The current is administered by placing a metal electrode over the thyroid gland, and securing it in place by bandage about the neck; or the patient may hold it in position against the thyroid with a towel. When the current is applied, the spark-gap must be just long enough to cause the tissues to vibrate energetically, but not sufficiently long to produce a tonic contraction in the sternomastoid and other muscles of the neck. This current should be administered for twenty minutes daily." I have been able amply to confirm the value of this form of electricity as an adjuvant in the treatment of exophthalmic goiter.

Conclusions on Electricity.—To summarize the remarks on electrotherapy, I would state that the most useful forms are the x-rays, simple galvanic, and the static wave current last mentioned. A thorough experience in the application of electricity is a vital qualification. Though in many instances we feel that the effects of electricity are largely psychic, when we observe benefit derived by many patients who are relatively insusceptible to suggestion, I feel that electricity possesses real value in a goodly percentage of patients. Employed alone, electricity is useless. It must never be regarded as a mainstay in treatment, but as a supplement to the necessary hygienic, dietetic,

medicinal, psychotherapeutic, and other measures employed in the treatment of these patients.

In the decision regarding the form of electricity to be employed in a given patient, extreme care and the most scrupulous individualization must be exercised. Some patients take x-rays well, others poorly. The same may be said of radium, the high frequency, and other currents. Even the very thought of receiving electricity in treatment may upset a very nervous patient to such a degree that it seems wisest to abandon the idea at once. In general, however, a bit of tact and persuasion will overcome the preliminary hesitancy, and a current can be discovered to meet individual indications. Electricity is rarely of any service during the very toxic stage of the disease, and if we are to employ it at all, it is best to await an amelioration of acute symptoms.

7. INJECTION TREATMENT OF HYPERPLASTIC GOITER

Injections of various substances into the thyroid gland have been practiced for many years, and though many successes are claimed for this method of treatment, it has fallen into general disrepute in the treatment of exophthalmic goiter. Such substances as tincture of iodin, chromic acid, iodoform, osmic acid, and other chemicals have been advocated from time to time. The purpose of injections is to reduce the size of the gland by the formation of areas of sclerosis. These substances are injected directly into the parenchyma of the gland, the needle being first employed to aspirate in order to determine whether a vein is reached. Sheehan reports favorable results from injections of *carbolic acid*, *iodin*, and *glycerin*. Five drops of equal parts of carbolic acid, C. P., tincture of iodin and glycerin are injected into the most prominent part of the goiter, usually at five day intervals. According to Sheehan, if five injections do not suffice, more can be given with perfect safety. At first, an inflammatory reaction occurs in the gland, followed by cicatricial adhesions and consequent obliteration of the cells. After the injection the patient complains of pain and swelling; the pain terminates into soreness in twenty-four hours. If the swelling and pain continue, codein in small doses, with ice applied over the goiter will give relief.

Quinine and Urea Injections are advocated by Watson to relieve hyperthyroidism, but not to remove the goiter. Although he claims that a small toxic or atoxic goiter may, through the reaction, disappear, the results are liable to be disappointing. The injection must be employed with discretion, as an inexperienced operator is liable to inject too deeply or to make the injection within the trachea, or is liable to produce alarming symptoms of hyperthyroidism which might result disastrously. He obtains the best results by keeping the patient in bed in a hospital for several weeks while giving the injections, the length of time

depending on the severity of the symptoms and response to treatment. A local anesthetic is employed at the site of injection. In order to prevent an acute attack of hyperthyroidism, the patient's threshold to stimuli is raised by means of preliminary injections at one to three day intervals, of a few minims of sterile salt solution followed by injections of sterile water, into the most prominent part of the thyroid. After two to four preliminary injections, the nervous reaction is so diminished that the quinin and urea can be given with only slight discomfort and no increase in symptoms; as soon as there is no hyperthyroidal reaction following the water injections, their usefulness is at an end. The quinin and urea injections are made into different parts of the tissue each time. An all glass syringe of 1 to 2 c.c. capacity is used, and after the usual aseptic precautions, the tissues down to the gland are anesthetized with a weak cocain or novococain solution. The syringe is now detached, and the needle is thrust carefully into the body of the goiter. After ascertaining that there is no fluid in the thyroid and that no blood or air comes through the needle, the syringe is attached and the infiltration slowly made. From 1 to 4 c.c. of a 30 to 50 percent. quinin and urea solution are administered at a treatment, repeating the injections about every third day, depending on the progress of the case. Watson administers eight to fifteen infiltrations. He suggests that the injections will not relieve the symptoms of advanced toxic goiter where the vascular and nervous systems have been permanently damaged. He further believes that the greatest field of usefulness for these injections will be found in those cases of beginning hyperthyroidism not severe enough to justify operative treatment, and as a preparatory measure to partial thyroideectomy in chronic cases of toxic goiter in which the patient is too ill to warrant any form of immediate operative procedure.

Boiling Water injections were introduced by Porter, whose technic is as follows: The skin and the area to be injected are thoroughly anesthetized by the injection of a free quantity of $\frac{1}{2}$ of 1 percent. novocain solution. One of Porter's steel syringes, taken out of the boiling cauldron, is filled with boiling water, which is immediately injected by inserting the needle into the substance of the mass. To prevent scalding, the skin and the contiguous surfaces are shielded by a covering of towels, leaving only the point of injection exposed. As the steam or water is apt to escape from the needle as it approaches the skin, a gauze swab is held as a shield in front of the needle, which later is thrust through and into the skin, when the contact is made. From 10 to 20 minims are forced out in one spot. The needle is then partially withdrawn, and the point carried to a new field, and the injection repeated. Three or four such areas may be injected at one sitting, and these may be repeated as required, in one or two weeks, and so on, until the tumor disappears. A Bunsen burner or an alcohol lamp held under the barrel of the syringe just as the needle is being inserted will insure a high temperature. It

is advisable not to have the point of the needle immediately under the skin, as the excessive heat so directly applied may produce necrosis, which is apt to become a point of infection. If the skin covering remains intact, all tissue coagulation or destruction, being aseptic, is harmless, and the solidified mass gradually disappears by granular metamorphosis. Important vessels and nerves, as well as the trachea, should be avoided.

In commenting upon these forms of treatment, Markoe states: "The use of quinin and urea is similar to the use of boiling water employed by Charles Mayo and others, and to the use of phenol and boiling water employed by Ochsner. The result of these injections is a marked edema in the tissues, sometimes with fatal issue. I think this result has occurred in 1 or 2 cases. Although Dr. Watson has reported some splendid results, I think we must sound a note of warning not to inject any of these substances at random. We may have the complication of acute edema with sudden death." Mayo states that he has had 3 patients die from the injections of boiling water. "They were treated in their beds to prevent shock, the water was probably not hot enough to coagulate albumin, and possibly more easily enabled the gland to throw off the hormones of secretion."

It can readily be seen that the injection treatment in true hyperplastic goiters is neither reliable nor safe. This mode of procedure may be very efficacious in nontoxic goiter, but in the vascular goiter of Graves' disease many things may happen in consequence, among which are acute hyperthyroidism, hemorrhage, infection, dangerous dyspnea, and sudden death from the injection of the substances into a blood vessel.

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CHAPTER XXIV

MEDICINAL TREATMENT OF EXOPHTHALMIC GOITER

THAT there have been advocated and employed between 200 and 300 drugs with varying degrees of success or failure in the treatment of exophthalmic goiter is not due to the absence of dependable drugs in this affection. The lack of concentrated attention to the subject of the medicinal treatment of the disease and the fact that the etiology and clinical manifestations of the affection require not standardization based upon specifics, but individualization in the broadest sense of the term, are the real causes of failure, doubt and discouragement in many quarters. In the consideration of the etiological and clinical features of a series of cases, though there may be discovered many features in common, there are observed more features of difference. The selection of drugs, as indeed of other measures, must likewise be based more upon the points of difference than the points of similarity. This is the essence of individualization; this is why the treatment of the disease is so baffling to those who have observed it superficially, and this is why the drugs to be employed advantageously in Graves' disease cannot be counted on the fingers of one's hands.

It is not true, however, that there are hundreds of drugs which might be employed successfully in the medicinal treatment of the disease. Many drugs employed from time to time are distinctly contraindicated in Graves' disease; some are of doubtful value in one patient and useful in another; still others are singularly serviceable in the majority of patients. We shall accordingly divide the discourse on the medicinal treatment of Graves' disease into (A) Drugs contra-indicated and of doubtful value; (B) Drugs serviceable in Graves' disease; and (C) Prescriptions advocated.

(A) DRUGS CONTRA-INDICATED AND OF DOUBTFUL VALUE

Thyroid Extract may be employed under one condition, *i.e.*, when, in a case of mixed hypo- and hyperthyroidism, evidences of the hypothyroidism predominate. It may also be employed in the myxedematous sequelæ of the "burned out" thyroid occasionally observed to follow an unusually chronic form of Graves' disease. Despite these indications, thyroid extract must be administered *cautiously* with a full understanding of the patient's history and symptomatology and of the potentiality

of the drug for harm. Though we receive occasional reports of the efficiency of the drug in typical Graves' disease, these instances are open to doubt (in diagnosis), and, at any rate, are no argument for its use. *Thyroid extract is contra-indicated in exophthalmic goiter*, and to administer it to these patients is comparable to an attempt at extinguishing a fire, not with water, but with gasoline. In common with other clinicians, I have observed disaster follow the use of thyroid extract in patients suffering with this disease. Finally, as pointed out by Coulaud and others, the possible presence of phthisis or diabetes in these patients is an added reason against thyroid ootherapy.

Adrenalin or epinephrin is likewise contra-indicated because of its stimulating influence upon thyroid secretion and the sympathetic nervous system. **Suprarenal medulla**, because of its adrenalin content, is contra-indicated for the same reasons.

Thymus Gland has been tried by many observers, eminently Owen, Mikulicz, Blondel, and others, but I have not been able to confirm its virtues. I agree with Pisani who believes that thymus is contra-indicated in Graves' disease, since, theoretically, it is an excitant of thyroid activity. The very fact that the thymus gland is in a hyperplastic condition in a large percentage of patients with Graves' disease would seem to speak strongly against the use of more thymus in treatment.

Parathyroid Extract, though harmless, is of doubtful value. It had been administered some years ago for the purpose of overcoming tremor and mental excitability.

Pituitary Gland (Anterior Lobe).—Despite the favorable reports of Richter and others, I have been unable to obtain any benefit in these patients through the use of anterior pituitary substance. **Tethelin** is a substance isolated from the anterior lobe of the pituitary body by Robertson. Though it has been advocated in the treatment of Graves' disease, there is no evidence to confirm its virtues.

Biliary ootherapy has been suggested with a view to slowing the pulse, but its efficacy awaits confirmation.

Insulin was injected for ten days by Lépine and Parturier into a patient presenting glycosuria and some evidences of exophthalmic goiter, with asserted good results. The tendency to arrive at hasty conclusions must here, as elsewhere, be guarded against.

Serum Therapy in the treatment of Graves' disease has had its days of prominence, but it may be stated in general that these substances are of questionable value. Serums were administered on the hypothesis that they are capable of neutralizing the excess of thyroid secretion in the blood and of overcoming the hyperactivity of the thyroid gland. The bull, sheep, dog, goat, horse and other animals are thyroidectomized and their serums prepared and standardized for administration. Among the preparations employed are: **Thyroidin** or **antithyroidin** prepared by Moebius from the serum of the sheep deprived of the thyroid gland

six weeks before the first serum is taken. **Rodagen**, the dried milk from thyroidectomized goats, was introduced by Lanz. **Rogers and Beebe** prepared a serum from two hyperplastic thyroids obtained from an autopsy of Graves' disease patients. They injected these into a rabbit, so that the nucleoprotein produced a cytolitic effect and the thyroglobulin an antitoxic influence. The serum obtained was administered to patients with varying degrees of success by Rogers and Beebe, who assert that this treatment is not to be employed if the chromaffin system is affected. Forchheimer states that this mode of treatment has no reason for existence and should never be used. Even **antidiphtheritic serum** is reported as having succeeded in relieving the symptoms of a few cases of exophthalmic goiter. Serum therapy, to repeat, has little, if any place, in the treatment of Graves' disease today.

Digitalis, despite the opinion of some observers, I find to be distinctly contra-indicated during the *active* stage of the disease. Digitalis, employed in Graves' disease, may serve somewhat to regulate a delirious heart or a heart in a state of flutter or fibrillation, but due caution must be observed lest the apparent good be overbalanced by harm. Digitalis *may* help, more often hinder, and at times render impossible, recovery from this disease. Sufferers from Graves' disease, singularly tolerant to large doses of quinin and its salts, are singularly intolerant to digitalis and its products. It does not reduce the heart rate, but, on the contrary, may indirectly increase heart hurry by its deleterious effect upon the digestive functions. I have seen this occur in dozens of patients under experimentation. We shall discuss the *indications* for digitalis later.

Opium and its derivatives,—morphin, heroin, codein, dionin, and the like,—are contra-indicated not only for their possible habit forming qualities, but also because they possess no real virtues in this affection, merely retarding elimination.

Iodin in *large doses* is generally contra-indicated, on the grounds that there is already an excess of iodin in the blood of these patients. However, minute doses may exert a salutary effect in isolated cases, and in rare instances, especially if syphilis be an etiological factor, moderately large doses may prove curative.

The Coal-Tar Products such as acetanilid, phenacetin, and the like, are contra-indicated because of their depressant influence upon the circulatory and respiratory systems.

Caffein should never be employed during active Graves' disease unless there is a very distinct indication for its use. This drug, in further whipping up the patient's cerebration, circulation and renal functions, and in aggravating the already troublesome insomnia, is capable of untold harm.

Strychnin is open to the same objections, unless, of course, there is a clear indication for its use, as, for instance, circulatory decompensation.

Alcoholic Substances are clearly contra-indicated, possessing no virtues, and capable of considerable harm in exophthalmic goiter.

Dechlorination was advocated a few years ago. Alt employed this treatment in 12 cases of Basedow's disease and claims to have obtained complete cures within a few months by his method. I have tried out this mode of treatment in a series of cases, with doubtful results.

Bromids may be employed, but are usually supplanted with distinct advantage by other substances. The dose of bromids required to overcome the insomnia, mental excitability, and other nervous phenomena observed in Graves' disease is great enough to produce bromism. This is the chief objection to its use.

Sulphonal, **Trional**, **Paraldehyde**, and **Chloral Hydrate** may all give way to veronal and luminal, which I find the best nerve sedatives to employ in Graves' disease. I have been unable to confirm the occasional good report from the use of **hyoscin hydrobromid**. This drug is too powerful a substance to be used for any length of time, and in some instances it aggravates rather than improves the symptoms for which it is given.

Oil of Sesame is advised by Swieicki for its ability to reduce the production of adrenalin.

Ergot, or rather **Ergotin**, is commonly employed in this disease for its possible controlling influence on the peripheral blood vessels, especially those of the thyroid. It was originally combined in doses of gr. i with the hydrobromid of quinin gr. v, in capsule form, administered t.i.d. Though I have never observed any untoward effects from its use, I have been unable to note greater improvement in patients taking ergotin than in those not taking this substance.

(B) DRUGS SERVICEABLE IN EXOPHTHALMIC GOITER

Quinin is one of the most useful drugs in this affection, for several reasons, among which are; (a) there are no contra-indications to its use; (b) it is capable of great good in the average patient; and (c) it is the basis of the quinin diagnostic test (see "diagnostic tests").

Nearly 40 years ago, Forchheimer called attention to the therapeutic virtues of quinin hydrobromid in exophthalmic goiter, results which have been amply confirmed by many observers since. To quote Forchheimer: "The good effects under this treatment usually follow in the same sequence: first, the tachycardia improves, the pulse frequently coming down from 130-140 pulse beats to 80 or 90 in forty-eight hours. Secondly, the thyroid gland diminishes in size by measurement. Thirdly, the tremor and exophthalmos disappear. In by far the greater number of cases the exophthalmos is the last symptom which disappears. To convince oneself that the treatment is the cause of the changes just noted, it is necessary only to withdraw the pills and, unless the patient

is cured, the symptoms recur. If after the withdrawal of the pills the symptoms disappear, such patients, as a rule, may be considered cured. . . . The treatment just described is most valuable in the mild attacks, the percentage of complete recoveries being very large and after a short time. When the fully developed form exists, either primarily or as a relapse, complete recoveries are the rule, but more time is required. When the patient has the foudroyant form the results are excellent."

Of the physiological action of quinin in Graves' disease we are by no means certain. It is probable that it counteracts the excess of iodin in the blood, lessens bodily catabolism, reduces temperature, enhances the elimination of purin bodies, contracts the peripheral arterioles, regulates the heart, and increases the threshold of reflex excitability. All these are highly desirable effects in this disease, thus rendering quinin a mainstay in the medicinal phase of the management of the average case.

Patients with Graves' disease are insusceptible to cinchonism. They may be given large doses—30 to 40 grains and more of the quinin daily for a long time, without untoward effects. Even in the presence of gastric and genito-urinary disturbances, quinin, especially the hydrobromid, may be given with impunity.

Pregnancy during the course of Graves' disease is no contra-indication to the administration of quinin; indeed, it is of vital importance to continue its administration during gestation in order that the Graves' syndrome be held in check in the interests of safety to the unborn infant. The hydrobromid of quinin is most often employed, but the sulphate and other salts of quinin may be employed if desired.

Quinidin Sulphate has been highly extolled for its influence on morbid cardiac function. Wenckenbach, in 1914, was among the first to call attention to its use in auricular fibrillation. There is today a rather voluminous literature pertaining to this subject, among which figure such names as Frey, Hewlett and Sweeney, Ellis and Clark-Kennedy, Benjamin and Von Kapff, Eyster and Fahr, Sappington, Wilson and Hermann, Viko, Marvin and White and others.

The physiological effects of quinidin are said to be about as follows: The drug depresses the vagus; by a reduction of vagal tone there is an increased power of junctional tissues to conduct, acting in a manner somewhat similar to that of atropin. Occasionally, vagal depression is marked and dominant, increasing the heart rate to a considerable degree. This is one of the objections to the use of the drug. Ordinarily, the rise of ventricular rate is moderated by an opposed direct action of the quinidin upon the junctional tissues. Quinidin thus increases the refractory period of auricular muscle, decreasing its irritability and its rate of conductivity. In those ordinarily susceptible to cinchonism (nonhyperthyroid patients) quinidin is better tolerated than quinin. Cardiologists have observed that the drug acts best on hearts

not seriously degenerated, while in very large hearts and in those in decompensation the drug is of little benefit. In nonhyperthyroid patients the following untoward effects have been observed: (a) cinchonism, (b) sudden heart failure, (c) sudden collapse, and (d) sudden death from embolism. Wilson and Hermann point out that embolism is probably due not to quinidin directly, but to the sudden cessation of fibrillation and the dislodgement of thrombi which had formed in the dilated fibrillating auricles on the resumption of normal auricular activity. However, embolism occurring during quinidin administration cannot be differentiated from embolism occurring spontaneously from chronic endocardial affections. Sudden death from embolism in these patients has occurred before quinidin became popular in treatment.

With a view to determining the effects of quinidin sulphate on the clinical picture of Graves' disease, especially tachycardia and auricular fibrillation, I made observations on 300 patients, extending over a period of 18 months (October, 1922, to April, 1923), and have been able to arrive at the following conclusions:

(1) Quinidin sulphate, if used up to 30 or 40 grains a day, does not produce cinchonism or other untoward effects in subjects of Graves' disease.

(2) It is inferior to the hydrobromid salt in its influence on the general symptomatology of the affection.

(3) Since auricular fibrillation incident to Graves' disease is usually paroxysmal and the auricles are not as badly dilated as in cases of primary organic heart disease, embolism through quinidin administration is a very remote possibility.

(4) However, quinidin exerts no special benefit in auricular fibrillation of Graves' disease.

(5) Quinidin does not increase, but, as with the use of quinin hydrobromid, tends to diminish the heart rate in Graves' disease.

(6) Quinidin sulphate may be given in lieu of the quinin hydrobromid in the medicinal treatment of Graves' disease, but the hydrobromid is more efficacious.

Can Quinin Be Administered Intravenously?—This question is frequently asked, and the response is often evasive or ambiguous. Intravenous treatment is, theoretically speaking, an attractive mode of therapy, since the digestive organs are spared, and the drug enters the circulation unchanged by the digestive juices and is more capable of prompt, direct contact with morbid tissues. Since Baccelli introduced the intravenous mode of quinin in the treatment of malaria in 1890, there have been many exponents of intravenous therapy. Conservatism, however, is now evident, and there are many observers whose experience has taught them to be guarded in their attitude on the question. For instance, the United States Public Health Service has recently issued a bulletin cautioning against the use of the intravenous injection of quinin

in the treatment of malaria. Cases of severe collapse have been reported following the procedure, and accidental extravasation into the tissues has caused local necrosis and sloughing. Aside from untoward results because of faulty technic, Voegtlins has sounded a note of warning regarding intravenous therapy covering many other vital points of interest. In a recent editorial of the *Journal of the American Medical Association*, we note the most important phase of the question well emphasized in the following words: "Even if the word faulty could be discarded in referring to current technic, if asepsis were inevitable, if subcutaneous, intramuscular and intravenous injections were made painless and perfect rather than bungling, there are hazards in intravenous routes that Voegtlins has clearly emphasized. The blood is not an indifferent fluid; it is a nicely 'balanced' solution. . . . We know today that the chemical composition of the blood and its physicochemical properties, such as osmotic pressure, hydrogen-ion concentration and colloidal state, are maintained with remarkable constancy and appear to be essential to physiologic well being. A sudden change in reaction, the production of precipitates and subsequent thrombosis in vital organs, the overwhelming of sensitive tissues such as the cardiac and nervous structures with high concentration of potent drugs—these are a few illustrations of the untoward possibilities. . . ."

The intravenous route for quinin administration in Graves' disease should not be employed for reasons other than those already implied. The procedure itself serves as an added shock to the extremely sensitive patient; the quantity so introduced is so small as to require two or three such injections daily, with multiple psychic trauma. Finally, these patients do not require the intravenous route for quinin medication, for they thrive very satisfactorily upon quinin administered by mouth.

Quinin is best administered in the form of the hydrobromid salt alone or combined with other drugs, in doses of gr. v to gr. viii in capsule, 3 or 4 times a day, preferably immediately before feeding, in order that the drug will emerge from the capsule on a full stomach.

Iodin, despite many views to the contrary, is very useful in Graves' disease, depending upon the method of administration. The old view that iodin administration stimulates the thyroid to further secretion and is therefore contra-indicated in cases of thyroid hypersecretion, is offset by the fact that there is a deficiency of iodin in the goiter, so that, theoretically, the introduction of iodin into the system results in a resting stage of thyroid function with consequent opportunity for the restoration of its physiologic balance. There is probably an additional unknown factor to account for benefit obtained by iodin administration in hyperplastic goiter. Perhaps a part of the credit due iodin in Graves' disease is because of its influence on the enlarged thymus, a tissue yielding readily to iodin therapy. Iodin not only causes the goiter to revert to the colloid state, but also assists in the absorption of patho-

logic tissue within the gland, and acts as an antitoxic to the intestinal tract, destroying certain contents which might bear etiologically upon the disease. It has been shown that the removal of part of the thyroid in an animal results in secondary hypertrophy in the remaining portion, with increased vascularity and increased colloid formation; if iodin is administered soon after operation, no hypertrophy occurs; or if iodin administration precedes operation, little or no hypertrophy occurs. Marine and Lenhart are also convinced that "in the presence of sufficient doses of iodin all true hyperplasia is prevented." They have used iodin in the form of the iodid of potassium, syrup of hydriodic acid and the syrup of the iodid of iron without untoward effects. Many other observers, namely, Delgado, Neisser, Loewy and Zondek, Beebe, and I have employed iodin in Graves' disease with distinct advantage. Labb  reports the favorable use of iodin in 5 cases of Graves' disease associated with diabetes mellitus, in which both affections were markedly benefited.

Plummer, and Plummer and Boothby believe that in exophthalmic goiter the thyroxin is incompletely iodized, rendering it a potent toxin. This is responsible for the rise in metabolism and many of the symptoms observed in the syndrome. Hence, in their opinion, the administration of iodin, preferably in the form of Lugol's solution, is indicated.

Personally, I feel that iodin may be tried with impunity in all cases of exophthalmic goiter, if results are carefully noted. Most cases of untoward effects seen are due to the *abuse* of iodin through lack of proper observation. Large doses are of course dangerous in nearly all cases and should be avoided, except where the disease seems to be of syphilitic origin, in which instances rapid improvement is seen. However, we meet with exceptional cases of exophthalmic goiter without evidences of syphilis in which, small doses proving harmless, the drug is cautiously increased, and the patient is finally cured. I was bold enough, in 1911, to administer gradually increasing doses of potassium iodid in a very severe case of Graves' disease with cardiac decompensation, and the patient is active and has been enjoying perfect health ever since. The dose was 5 grains, three times a day, increasing the dose by 1 grain daily. There being a tolerance to the drug and manifest improvement, it was continued until the patient was taking 1 drachm of iodid three times daily. Catarrh of the larynx caused me to discontinue the drug for two weeks, when I again prescribed 5 grains thrice daily, increasing the dose as before to 1 drachm. The goiter gradually disappeared, and the marked exophthalmos, tachycardia, tremor, and other symptoms were greatly ameliorated in a few weeks. Within six months he gained 20 pounds, and within fourteen months he was discharged from treatment subjectively and objectively recovered. There were no evidences of syphilis.

I prescribe iodin in the following forms: The hydrarg. protiodidi in grains $\frac{1}{20}$ to $\frac{1}{10}$; syr. ferri iodidi in gtt. xx to xl; the sodium or potas-

sium iodid in grains ii to v; or the tr. iodin in gtt. i to iii. These may be given once, twice, or three times a day.

Finally, it must be emphasized that patients to whom iodin is administered must be kept under observation and examined at least once a week. While this drug is exceedingly useful in a large percentage of these patients, an occasional patient is made worse. We must therefore be on our guard lest the patient in whom we are about to decide iodin to be contra-indicated stops treatment abruptly but continues to take the "medicine."

Whole Pituitary Gland.—I have already stated that *anterior pituitary* substance has, in my experience, at least, been found wanting in therapeutic properties in the treatment of Graves' disease. *Whole pituitary* is more serviceable, probably because of its posterior pituitary content. It may be given by mouth in doses of 1 to 2 grains two or three times a day.

Posterior Pituitary is of singular service in Graves' disease, appearing to exert a check upon excessive thyroid and adrenal activity. Solis-Cohen, Pal, Hector Mackenzie, Barr, and others have reported excellent results from posterior pituitary. The substances may be given by mouth, in grains $\frac{1}{4}$ to i, two or three times a day. I have found this substance quite serviceable when given in capsule form alone or combined with other drugs. In a recent article, Hamill, as a result of experiments on cats, confirms the clinical observations in Graves' disease that absorption of pituitary extract administered by mouth gives rise to characteristic reactions, and that absorption from the stomach takes place more rapidly when the organ is full and during active digestion. He advocates its administration in solution rather than in solid or powder form. In severely ill patients, I prescribe posterior pituitary (pituitrin) intramuscularly, in doses of 5 to 20 minims once, twice, or three times a day, according to indications. In many instances, especially in sympatheticotonia, results are prompt. The nervousness, tachycardia, thyroid swelling, exophthalmos and weight are favorably influenced, and the patient may make rapid strides toward recovery within a few weeks. However, in other instances, results are disappointing. Here again it is a matter of individualization. Whole or posterior pituitary is contra-indicated in arteriosclerosis, hypertension, advanced myocarditis, and in the presence of diarrhea.

It is well to add here that during threatened or actual circulatory decompensation, posterior pituitary by hypodermic administration is the most serviceable drug in our armamentarium. It not only adds tonus to the myocardium, but also to the entire circulatory tree, raising the systolic blood pressure to a level more consistent with safety.

Suprarenal Gland is both harmful and useful, depending upon its method of use. Solis-Cohen (1897), Crary (1898), and Potts (1902) are among the first to call attention to suprarenal otopathy

in Graves' disease. More recently, Shapiro and Marine, Obregia, Kantor, Black, Hupper and Rogers have made further report on this subject.

Theoretically, suprarenal *medulla*, because of its epinephrin content, is contra-indicated in Graves' disease, and clinical experience amply confirms this view. Patients treated with suprarenal medulla or with epinephrin are made worse, as these are excitants of thyroid secretions and of the sympathetic nervous system. Suprarenal *cortex*, however, contains an antagonist to epinephrin, its physiological action probably being that of depressant to the thyroid secretion and the sympathetic nervous system. It probably increases the iodin content of the thyroid, thus discouraging hyperplastic changes within the organ. However that may be, I have been able to confirm the reports of Shapiro and Marine relative to its virtues, and have seen strikingly beneficial results in a goodly percentage of cases through its use. The extract of the whole gland is, however, likewise of service, as its contained epinephrin antagonist in the cortex overcomes theoretical objections.

Suprarenal opotherapy is especially useful in instances of extreme asthenia and low systolic blood pressure. The extract of the whole gland may be administered in doses of grains iii to v, two or three times a day. It may also be administered in the form of the glycerin extract of the fresh product. The cortex may be given in somewhat the same dosage. Adrenal nucleoprotein and adrenal residue may also be prescribed.

There is one indication for epinephrin or adrenalin in Graves' disease, and that is, the diarrhea occurring in a percentage of cases at certain periods during the course of the affection. A rectal injection of 30 drops of adrenalin chlorid (1:1000) solution in 200 c.c. of water produces no systemic effects, and is the most effectual method of overcoming this troublesome symptom. The enema may be repeated two or three times. Usually the first injection suffices to cause a cessation of bowel movements for approximately 20 hours.

Ovarian Extract and Corpus Luteum occupy an important place in the medicinal treatment of the disease for two reasons: First, they antagonize the thyroid secretion, and second, in Graves' disease there is ovarian hyposecretion. So that therapy with ovarian extract or with corpus luteum would serve both to neutralize thyrotoxemia and as a substitute for deficient ovarian secretion. Moreover, corpus luteum overcomes the hypertension frequently present in Graves' disease. Coulaud, among others, has found ovarian treatment of service. However, I have been unable to confirm the very sanguine views of Hoppe, who finds that "the treatment of hyperthyroidism with corpus luteum is comparable with the treatment of myxedema with thyroid extract." In my experience corpus luteum alone is scarcely capable of tangible results. Combined with quinin hydrobromid and other drugs, however,

it appears to serve as an excellent synergist in treatment. I prescribe corpus luteum in doses of gr. iii to v, t.i.d.

Testicular Extract in male subjects of Graves' disease possesses no special value, though it seems to exert some "tonic" effect. At best, it cannot compare with corpus luteum in female subjects. It may be given in doses varying from gr. ii to v, t.i.d.

Pancreatic Extract is of service, especially in cases associated with symptoms of apparent pancreatic insufficiency, *i.e.*, glycosuria, polyuria, bulimia, polydipsia, fat in the stools, etc. Pancreatic extract may incidentally overcome nausea and vomiting and improve nutrition by correcting starch indigestion. Since the pancreas is physiologically opposed to the thyroid, its administration is based upon logical grounds. Pancreatic extract is best administered in the form of pancreatin in 5 grain doses after meals.

Lactic Acid Ferments are employed by McCarrison and others on the theory that hyperthyroidism is largely due to auto-intoxication. Pietrowicz, in 1916, observed a marked influence on the Graves' syndrome with a considerable slowing of the heart and decided diminution in the severity of the nervous and gastro-intestinal symptoms by the use of buttermilk and lactic acid ferments. Patients with Graves' disease may be given lactic acid bacilli in tablet form with advantage. At all events, buttermilk containing the bacilli in sufficient number should constitute an important element in the dietary.

Intestinal Antiseptics are advocated by McCarrison as efficacious in the treatment of exophthalmic goiter in cases which appear to be of intestinal origin. He advises *thymol* in 10 grain doses or more, night and morning, administered in the form of a coarse powder which is washed down with a draught of water. The bowels are kept active by a suitable laxative, and all solvents of thymol are excluded from the dietary. I have found intestinal antiseptics more serviceable in the simple forms of goiter than in Graves' disease.

Veronal and **Luminal** are, in my experience, the most satisfactory sedatives to be employed in this disease. Though these drugs are usually employed in single doses at bedtime and may be employed in this manner in these patients, I have, during the past ten years, employed these substances in small doses 3 or 4 times a day, combined in capsule with other drugs. This mode of administration is by far the most satisfactory. Mental excitability and irritability is reduced, thus indirectly reducing the heart rate and increasing the sense of general well-being, and when the patient retires at night, the cumulative effects of the drugs are sufficient to overcome insomnia and nocturia, and render sleep refreshing. Given in this manner, I cannot praise these substances too highly as the most useful drugs in existence for overcoming the nervous manifestations of Graves' disease.

The dose varies with the degree of nervousness and insomnia and

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with the idiosyncrasies of the patient. I prescribe veronal in doses of gr. i to iii, or luminal gr. $\frac{1}{3}$ to i, three or four times a day. Usually, 2 grains of veronal or $\frac{3}{4}$ of a grain of luminal per dose serves the purpose. I have never observed any untoward effects from the use of these drugs administered in this manner.

Belladonna and **Atropin** fulfill several needs in the medicinal treatment of Graves' disease. I agree with McGuigan in his statement that small doses of atropin slow the heart rate. This is produced by its effect on the vagus center in the medulla and a possible stimulating effect upon the vagus endings. To obtain this effect, the dosage of atropin sulphate should be gr. $\frac{1}{250}$ to $\frac{1}{50}$, two or three times a day. McGuigan points out that larger doses of atropin (gr. $\frac{1}{60}$) still cause slowing, with a tendency to irregularity. This dosage, however, has in my experience, led to vagal depression if given oftener than once daily. Atropin sulphate in larger doses increases the heart rate by a paralyzing effect upon the vagus. Belladonna and atropin in moderate doses are useful in cases of marked vagotonic manifestations. In gastro-intestinal irritability atropin in gr. $\frac{1}{100}$ repeated according to indications is of signal service. It helps also to overcome some of the nervous symptoms. The tincture of belladonna is useful in the bladder tenesmus commonly complained of by these patients. In cases of extreme hyperidrosis the extract of belladonna, gr. $\frac{1}{6}$ to $\frac{1}{3}$, two or three times a day yields excellent results. It is important, however, to administer the drug cautiously to avoid the full physiological action.

Eserin or **Physostigmin** has been lauded by Moutier, and Lian and Welti, who called attention to this drug as useful in the tachycardia and palpitation of Graves' disease. It is highly serviceable in patients presenting clinical symptoms of marked sympatheticotonia with epigastric discomfort, nausea, and constipation. Though incapable of reducing the heart rate to any considerable extent, I have found the drug of service in overcoming the sympatheticotonic symptoms referable to the gastro-intestinal tract. Eserin salicylate or sulphate may be given in doses of gr. $\frac{1}{60}$ to $\frac{1}{50}$, two or three times a day, alone or combined in capsule with other medicaments.

Calcium is distinctly indicated in Graves' disease, since there is a deficiency of calcium in this affection. It should be administered prior to operation in instances of the removal of infectious foci, in order to avoid excessive bleeding, and prior to parturition in Graves' disease subjects. In the general therapy of these patients, Barr, Edmunds, and others have called attention to the merits of calcium as exerting a powerful influence on metabolism. The lactate is the most commonly prescribed salt. I have been prescribing *calcium glycerophosphate* in grain v doses, in capsule, t.i.d., alone or combined with other drugs.

Phosphorus is a very useful drug in the armamentarium of the internist treating Graves' disease, especially in view of the fact, as Grobly

remarks, that there is a general diminution of nucleoprotein formation in this affection. It may be administered in combination with cod liver oil or with other drugs in capsule form. I usually administer phosphorus in the form of lecithin.

Lecithin is well borne by these patients and yields excellent results. Berkley, in 1908, pointed out the singular potency of lecithin for great good in cases of Graves' disease, stating that these patients cling to the remedy "as an opium habitué clings to that drug." There is an amelioration of nervousness, a gain in weight, a lessening of the heart hurry and tremor, and a general sense of well-being. As in the case of other drugs, lecithin alone is not a mainstay; it is merely a very useful adjuvant to be employed in combination with other measures. Lecithin may be administered in alcoholic solution in doses corresponding to gr. $\frac{1}{100}$ of phosphorus, but it is best given in solid form, in doses of gr. ss to ii, combined with other medicaments.

Ichthyol has in my experience proved of brilliant service in exophthalmic goiter. How it exerts its beneficent effects I am unable to conclude, but the results obtained are somewhat similar to those of the quinin salts. It improves appetite and digestion, and is as good a means of increasing weight and a sense of well-being as any drug employed in this disease. In combination with quinin it becomes a very powerful formula, controlling the cardinal symptoms more promptly than anything I have ever used. At times patients rebel against taking ichthyol because of distasteful eructations, but this objection soon disappears, and a tolerance is acquired.

Arsenic, because of its reputed depressant effect upon thyroid secretion and its hematinic properties, may be combined with other drugs in the treatment of these patients. I prescribe it in the trioxide in doses of gr. $\frac{1}{100}$ to $\frac{1}{30}$, or in the form of the arsenate of iron, in doses of gr. $\frac{1}{16}$ to $\frac{1}{10}$, combined with other drugs.

Mendel reports good results in a series of cases treated with a combination of arsenic and iodin intravenously. Aside from the psychic factor which must always be taken into account in Graves' disease, the intravenous administration of drugs is not devoid of dangers.

Antisyphilitic Treatment is of course to be instituted in patients presenting evidences of syphilis. Graves' disease is, however, not commonly seen in syphilitic patients. Occasionally, one is apt to obtain prompt results through the use of salvarsan with or without the old-fashioned mixed treatment of iodids and mercury. Among others, Simonton, Roorda-Smit, and I have been able to effect recovery in Graves' disease of undoubted syphilitic origin by antisyphilitic treatment.

Iron may be employed on general principles. Aside from its hematinic qualities and its general benefit, it may assist in controlling diarrhea. In the presence of constipation some caution should be exer-

cised in its administration. The carbonate, or the pyrophosphate, in doses of grains i to iii, may be given t.i.d. The syrup of the iodid of iron and the arsenate of iron are mentioned under iodin and arsenic respectively.

Sodium Phosphate has long been thought to possess properties antagonistic to the toxemia of Graves' disease. Whether or not this is true, it is the safest laxative to employ in these patients, and its administration in doses of 1 drachm in a tumberful of hot water every morning enhances the possibilities of recovery by its favorable influence on the liver and bowels, stimulating these emunctories to full physiologic function.

Sodium Salicylate in 10 grain doses four times a day has resulted in benefit in the hands of a few observers. Anders reports a few cases in which there was almost total relief by the use of sodium salicylate. This substance is, of course, of greatest assistance in cases presenting a rheumatic etiology. Moreover, it has been observed that this drug occasionally produces a bradycardia when employed in rheumatism. It probably exerts a stimulating influence on the vagus.

Oil Injections into the bowel are suggested by Ebstein as essential in every case of exophthalmic goiter, in order to remove all impacted feces which may be the cause of constipation or diarrhea. This author reports four cures by this method. It is doubtful whether this alone cured these patients, though the remedy itself is highly laudable in a large percentage of instances.

Digitalis is serviceable, not during the active stage of the disease, but *during convalescence* in the presence of a still remaining tendency toward heart hurry despite obvious general recovery. In other words, digitalis, if it is needed at all, is only useful in the absence of active Graves' disease, *i.e.*, during the "passive stage." By the "passive stage" is meant that period during the course of the affection when the basal metabolism is less than plus 15, the patient is gaining rather than losing weight, and there is subjective and objective improvement. Ordinarily, when, after several months of properly applied nonsurgical management of a given patient, there is a restoration of weight, marked improvement in or disappearance of the thyroid swelling and of exophthalmos, and recovery of the central and peripheral nervous system,—in a word, when the patient thinks, acts, and appears normal, the heart rate, too, is returned to normal. Occasionally, however, the heart rate is still 90 or above, its restoration seeming to lag for an indefinite time behind the general improvement or recovery elsewhere. This is by no means an indication of failure in treatment; it is seen in tardy convalescence from other illnesses, notably influenza, typhoid fever, and pneumonia. The myocardium is still in a state of disturbed function; its nervous mechanism is still in a state of disequilibrium. Possibly the so-called morbid habit of tissues plays its part; if a whole individual can acquire

a bad habit, surely a part may also acquire a bad habit, necessitating correction—and the most efficient corrective here, at this time, is digitalis. To repeat, it is when the patient seems entirely recovered, when everything appears normal but the heart rate, that digitalis is indicated and is efficient as a restorer of vascular stability. It is then that the patient not only tolerates the drug but responds promptly to its action.

The drug having accomplished its purpose within 3 or 4 weeks, its service seems no longer to be required, and it is withdrawn. In the majority of patients, the heart rate will now remain normal. Occasionally, the rate will soon again extend beyond normal, though not to the previous figure. Digitalis is again administered for a like period, after which it may be withdrawn permanently. In rare instances, it may be necessary to prescribe the drug during 3 or 4 such periods with intervals of a week or two, depending upon individual circumstances, especially the previous severity and duration of the disease and the damage it has wrought upon the myocardium and its regulating mechanism.

I have found a fresh, well standardized extract of the leaves serviceable, in that it can be combined in capsule with other ingredients then employed. The dose varies with the age and prevailing circumstances of the individual. I find that $\frac{1}{4}$ to $\frac{1}{2}$ grain t.i.d. is quite sufficient in the average patient. Under no circumstances should we administer a quantity of the drug corresponding to an overdosage. It is far preferable to give too small a dose and await results than a so-called physiological dose in which results seem prompt, but in which there is danger of deranging the recently recovered but still delicately balanced circulatory and gastro-intestinal systems.

In the presence of symptoms of impending or existing circulatory decompensation, **digitalin** hypodermically or intramuscularly in doses of gr. $\frac{1}{2}5$, three or more times a day, according to indication, may be tried. Under such circumstances, digitalin may serve its purpose in assisting restoration of compensation, but the heart *rate* is little, if at all influenced. Posterior pituitary by hypodermic administration is also of service in circulatory decompensation. The measures, however, are of real service only as supplements to the other measures outlined in the broad management of Graves' disease.

Incidentally, such drugs as **spartein sulphate** and **strophanthus**, while they are rarely efficacious in overcoming the heart hurry of active Graves' disease, may, however, be employed in desperate cases without the fear of the untoward effects observed under like circumstances following the administration of digitalis. Spartein sulphate may be given in doses of gr. $\frac{1}{4}$ to i., alone or combined with other drugs, in capsule form, t.i.d. Strophanthus, in tincture, may be given in doses of gtt. v to x, t.i.d. These drugs are of distinct service during the "passive stage" of the disease and may be employed instead of digitalis. **Strophanthin** by

intravenous route as recommended by some in the treatment of heart failure should never be employed in the presence of Graves' disease.

(C) PRESCRIPTIONS RECOMMENDED

Having discussed the drugs most likely to be of service in the medicinal management of Graves' disease, let us now see what combinations of these may be given in the form of prescriptions. The possible number of formulæ with regard to variations of ingredients and dosage is large because, to repeat, the principle of individualization should dominate the mind of the medical attendant.

As I find that the majority of patients prefer capsules, the greatest number of formulæ will be written for capsules not exceeding a total of 10 grains of ingredients in each. Here we must mention an important point in capsule prescribing, namely, that many patients, especially subjects of Graves' disease and those otherwise nervous, find the capsule "sticking in the throat" even after an attempt to wash it down with a tumblerful of water. The capsule is lodged somewhere between the epiglottis and the cardiac end of the stomach, giving rise to a reflex flow of hydrochloric acid and symptoms of hyperacidity and indigestion. Thus patients are apt to complain that the capsules do not agree; that they cause indigestion and great discomfort. For this reason, and unless there are strong reasons to the contrary, I order capsules taken *immediately before meals* in order that the meal itself push them down into the stomach. Thus a capsule, formerly regarded by the patient as "medicine which does not agree" becomes entirely agreeable. Occasionally, a patient cannot swallow a capsule, no matter by what effort. Under these circumstances, powders may be prescribed. In quinin containing formulæ, powders are rather distasteful, but the addition of saccharin will overcome this objection. Liquids occupy a minor rôle in these formulæ, and may be given to overcome such symptoms as bladder irritability or gastric disturbances.

At the first consultation any medication in a given patient is tentative—more or less in the nature of a therapeutic test. Though, as a rule, the internist experienced in the treatment of Graves' disease will prescribe during the initial visit a formula which yields substantial subjective and objective benefit, he will be capable in many instances of improving his subsequent prescriptions as a result of further study of the patient. Finally, perhaps at the termination of a few weeks, the internist will be in position to prescribe substances yielding the maximum of benefit to his patient. From time to time, depending upon unforeseen circumstances, acquired immunity to drugs, and improvement in the clinical picture, prescriptions must be altered with regard to ingredients given, the dosage, or both. Hence, individualization in prescription writing concerns not only (a) discrimination between

patients, but also (b) response to various drugs at different periods in the course of the disease in the same patient, and (c) the need of variations in dosage at different times during progress toward recovery.

Forchheimer's original prescription is the following:

Formula 1: Rx Quinin Hydrobrom. gr. v
Ergotin gr. i
In capsule or pill t.i.d.

This prescription deserves great credit for its quinin content, but as it stands, I find it incapable of prompt results. In general, I find the following formula preferable:

Formula 2: Rx Quinin Hydrobrom. gr. v
Corpus luteum gr. iii
Veronal gr. iss
In capsule 3 or 4 times a day.

In male patients, the corpus luteum may be omitted, or it may be replaced by testicular extract. Instead of veronal, luminal may be given in dose gr. $\frac{1}{2}$ to each capsule. Thus the formula in a male patient might read as follows:

Formula 3: Rx Quinin Hydrobrom. gr. vii
Pulv. Orchic extract gr. iiiss
Luminal gr. ss
In capsule 3 times a day before meals.

In patients with marked insomnia, the veronal in grains vii or luminal in grains ii or iii may be given in single dose an hour before bedtime, these substances being omitted from the prescriptions mentioned.

In the presence of secondary anemia requiring attention, the formula may include iron or arsenic in one of the following combinations:

Formula 4: Rx Quinin Hydrobrom. gr. vii
Massa ferri carb. gr. ii
Arseni trioxidi gr. $\frac{1}{40}$
In capsule 3 times a day, before meals.

Or

Formula 5: Rx Quinin Hydrobrom. gr. vii
Lecithin gr. ii
Ferri arsenias gr. $\frac{1}{10}$
In capsule 3 times a day, before meals.

Or

Formula 6: Rx Quinin Hydrobrom. —
Calcii glycerophos. a.a. gr. iv
Massa ferri carb. gr. iss
Arseni trioxidi gr. $\frac{1}{40}$
In capsule 4 times a day, before meals and at bed time.

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The above formulae may be so written as to include a small dose of veronal or luminal if necessary.

The treatment of digestive disturbances has been discussed in the chapter on diet. Poor appetite and sluggish digestion may be improved by these formulæ:

Formula 7: Rx Calcii Glycerophos. —
Pancreatin —
Quinin Hydrobrom. a.a. gr. iiss
Ichthyoli gr. ss
Arseni trioxidi gr. $\frac{1}{100}$
In capsules before and after meals (6 capsules daily).

Or

Formula 8: Rx Calcii glycerophos. —
Pancreatin a.a. gr. iv
Lecithin gr. i
Ferri arsenias gr. $\frac{1}{10}$
In capsule 3 times a day, before meals.

Ordinarily, however, the appetite and digestion of these patients require no special consideration, improving with general improvement of the patient. The ichthyol content of a prescription may be increased gradually until 2 or 3 grains in each capsule are taken. Of course, it must be borne in mind that the total ingredients in a capsule should not exceed 10 grains. Because of their pancreatin content, the above two prescriptions serve also to improve carbohydrate tolerance.

Constipation may be overcome by sodium phosphate, but when this does not suffice, aloin may be included in these formulæ. The dosage must be small, because of the tendency of this substance to give rise to intestinal discomfort. I find gr. $\frac{1}{20}$ to $\frac{1}{10}$ sufficient. The addition of eserin in doses of gr. $\frac{1}{100}$ to $\frac{1}{60}$ will likewise tend to correct constipation.

Diarrhea, as already mentioned, may be controlled by the administration of bismuth, tannigen, or by enemas containing adrenalin chlorid.

Excessive sweating, a rather troublesome complaint, may be controlled by adding belladonna or atropin to the prescription as follows:

Formula 9: Rx Quinin Hydrobrom. gr. v
Luminal gr. $\frac{1}{2}$
Ext. Belladonnæ gr. $\frac{1}{6}$ to $\frac{1}{4}$ vel Atropin Sulph. gr. $\frac{1}{150}$ to $\frac{1}{100}$
In capsule 4 times a day.

The belladonna or the atropin, as the case may be, should be omitted from the prescription just as soon as the hyperhidrosis is improved.

Amenorrhea is common in Graves' disease and improves spontaneously when the general syndrome of the disease is ameliorated. Should

menstruation be unduly tardy in reappearing, thus worrying the patient, ergotin or manganese dioxidi may be added to the prescription as follows:

Formula 10: Rx Quinin Hydrobrom. gr. v
 Corpus luteum
 Manganese dioxidi a.a. gr. ii
 Ergotin gr. i
 In capsule 3 or 4 times a day.

Tachycardia ordinarily requires no special treatment, and, indeed, responds to none, excepting a broad general management of the disease itself. Should the heart rate become excessive, however, the following formula may be employed with a consciousness that *something* is being done for this symptom:

Formula 11: Rx Quinin Hydrobrom. gr. v
 Ergotin gr. i
 Spartein sulph. gr. ss
 Eserin salicylas gr. $\frac{1}{100}$ to $\frac{1}{60}$
 Luminal gr. ss
 In capsule 3 or 4 times a day.

Remark: In the presence of diarrhea, eserin should be omitted.

In persistent heart hurry, during convalescence (not during active Graves' disease) in those unusual instances in which the heart hurry persists after all other evidences of the disease have disappeared, digitalis is of service and may be combined as follows:

Formula 12: Rx Quinin Hydrobrom.
 Calcii glycerophos. a.a. gr. iv
 Ext. Digitalis foliorum gr. $\frac{1}{4}$
 In capsule 3 or 4 times a day.

The heart under these circumstances responds perfectly to digitalis therapy, and the drug may be withdrawn permanently within a few weeks.

In the presence of impending or actual cardiac decompensation with or without auricular fibrillation, the following may be employed:

Formula 13: Rx Quinin Hydrobrom. vel. quinidin sulph. gr. v
 Spartein sulph. gr. ss
 Digitalin gr. $\frac{1}{25}$
 Pulv. gland. Hypophysis (posterior) gr. i
 Luminal gr. ss
 In capsule 4 times a day.

Instead of including them in capsule, digitalis and strophanthus may be tried separately in liquid form, as follows:

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Formula 14: Rx Tr. Digitalis foliorum
Tr. Strophanthus a.a. fl. oz. ss
Sig.: 10 to 20 drops in water, t.i.d.

Tr. iodin may be combined with the above formula as follows:

Formula 15: Rx Tr. Digitalis
Tr. Strophanthus a.a. fl. dr. iv
Tr. Belladonnae fl. dr. ii
Tr. Iodin fl. dr. i
Aquaæ Dest. q.s. ad fl. oz. iii
Sig.: Teaspoonful in $\frac{1}{2}$ tumblerful of water t.i.d.

Or digitalin and the pituitrin may be given intramuscularly. However, cardiac decompensation and auricular fibrillation, unless the myocardium is very seriously damaged, require no special treatment, responding well to carefully planned measures calculated to overcome the Graves' syndrome.

Many patients are kept awake by bladder irritability and require to void as often as a dozen times each night. While the luminal and veronal in the capsules quiet the bladder reflex sufficiently to permit satisfactory rest, special treatment may become necessary. I have found the following formula of service for this indication:

Formula 16: Rx Sodii brom. 5 iv
Tr. Hyoscyamus fl. dr. vi
Aquaæ Camphoræ fl. dr. vi
Liq. potassii citratis q.s. ad fl. oz. vi
Sig.: 2 teaspoonfuls in water 3 or 4 times a day.

This prescription is discontinued at once following the relief from nocturia.

It is not always necessary to prescribe quinin in exophthalmic goiter. In a considerable number of patients, quinin, though harmless, is useless. Rarely, perhaps in 0.5 percent. of patients, there results a dermatitis from the use of quinin. Perfect individualization must recognize this fact. A change from quinin to organic products of known value in Graves' disease may be employed. Among these are corpus luteum, pancreatin, suprarenal cortex and posterior pituitary. These four may be given singly or combined as follows:

Formula 17: Rx Corpus luteum gr. iii
Pancreatin gr. iv
Ext. gland. suprarenal. cortex gr. ii
Ext. Hypophysis (posterior) gr. i
In capsule 3 times a day.

As mentioned elsewhere, the pituitrin frequently yields better results if administered by intramuscular injection once, twice, or three times a day as indicated.

Iodin may be given to most of these patients, but due caution must be taken by the medical attendant regarding idiosyncrasy, and the patient must be warned to return for observation as often as he is instructed to do so. It may be given in the form of hydrarg. protiodidi gr. $\frac{1}{20}$ to $\frac{1}{10}$, combined in any capsule formula. I find the best form of administering iodin is in the tincture, in gtt. 1 to 3, in a half tumblerful of water or milk, to follow immediately upon the capsule, 3 or 4 times a day. I have never observed any untoward results from iodin administered in this way. I have seen hyperplastic goiters formerly rather persistent and stubborn, soften and shrink promptly with iodin given in this manner as an adjuvant in treatment. The sodium or potassium iodid may be given in the same dosage if desired.

To summarize, I would state that in any new case of Graves' disease of moderate severity with no outstanding indications for treatment of special symptoms, a combination of two or more of the following drugs may be prescribed on probation: Quinin hydrobromid, corpus luteum, suprarenal cortex, calcium glycerophosphate, luminal, veronal, the protiodid of mercury, iron and arsenic. It must be remembered that no drug or combination of drugs can be considered useful in a given patient unless a period of trial of at least a few weeks has been given. Occasionally, the internist may be at his wit's end at prescription writing in a stubborn case, simply because the patient does not seem to respond favorably to treatment. This confirms our premise that drugs are not a mainstay in the management of Graves' disease. In the usual instance of lack of response to drugs there is something else lacking in the treatment of the patient. It is this something that should be sought for and supplied.

In concluding these remarks on the medical treatment of Graves' disease, I can do no better than call the reader's attention to the fact that examination of the prescriptions recommended will prove that the number of drugs employed as useful in Graves' disease is comparatively few. There is no need to experiment aimlessly with the numerous drugs of questionable virtue and waste valuable time for the patient.

The above suggestions are the result of intensive study of the treatment of Graves' disease since the year 1909, embracing the clinical observation of many hundreds of patients who have recovered through nonsurgical measures and whose permanency of recovery is confirmed by occasional observation during a period of years after discharge from active treatment.

Finally, it must be reiterated that drugs, though highly useful and necessary, are rarely capable *alone* of effecting recovery from Graves' disease. It is *rest* plus *diet*, with occasionally *electricity* and other minor measures, plus *drugs*, and last, but by no means least, *psychotherapy*, that constitute, in brief, the broad régime of the nonsurgical

management of this affection. It is to the consideration of psychotherapy that we shall apply ourselves in the next chapter.

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CHAPTER XXV

PSYCHOTHERAPY IN THE MANAGEMENT OF EXOPHTHALMIC GOITER

"A man's body and his mind, with the utmost reverence to both I speak it, are exactly like a jacket and a jacket's lining;—rumple the one,—you rumple the other."

A STUDY of the pathogenesis and symptomatology of the syndrome leads to the inevitable conclusion that in Graves' disease the mind is quite as ill as the body. The evident psychic dominance of the predisposing and exciting etiological factors, the psychic manifestations in the symptomatology as evidenced by the quickening of the mental faculties and the tendency toward the psychoses, the comparative ease with which, by mental suggestion, the syndrome is markedly aggravated or improved, and, reflexly, by the same means, the striking functional changes noted in the gastro-intestinal tract, skin, genito-urinary tract and elsewhere,—all these and many more facts indicate that the patient's self claims the attention of the physician quite as much as the disease. And if we agree that coöperation of the patient in treatment *must* obtain at any cost, we conclude that the psychic factor in the therapeusis of this disease is the foundation upon which the success of all other therapeutic efforts rests.

GENERAL REMARKS ON PSYCHOTHERAPY

The psychic factor in medicine has been sadly neglected, at the cost of the patients' welfare and the prestige of the profession. There are innumerable medical *scientists* in existence, but too few *physicians* who practice on the principle that the patient as well, not the disease alone, requires assistance. The human brain is infinitely more delicate in structure and function than the body; how much more likely it is to lose its functional balance and require adjustment! Interest in speculative phases of causal relationship in disease is necessary; a keen understanding of postmortem findings and of microscopic specimens is likewise imperative in the advancement of science. But the quest for cold science at the expense of the living human element is an error. To ignore the phenomena of the thinking mind and have everything subserve pathological investigation and scientific precision

in diagnosis is to concur with the surgeon in the time-worn assertion: "The operation was very successful, but the patient died." To study the patient is one thing; to cure him is another.

This indifference to the mental side of medicine is responsible for the existence of the many new cults which are an insult to the intelligence of sensible people, and certainly to the medical profession. This lack of mental, in combination with physical healing is the "something wrong" with the medical profession. The laity, hungry for that which the profession does not supply, eagerly accepts the new codes and creeds of Christian Science, Couéism, chiropractics, and the various other cults and "isms" cropping up constantly. For every person assisted to better mental health by quackery there are probably six who are injured; meanwhile, the mentally improved become press agents for the quack, and the buried patients are not about to deride. The situation is, to repeat, due to the lacking "something" in the medical profession; it is due to the scientific interest with its mental myopia, at the expense of a broad, interested perspective of the patient himself. The *usual* results obtained by the average physician in the management of a case of exophthalmic goiter is a striking example of proof of our premises.

Interrelation of Body and Mind.—The reason for the study of the mind in medicine becomes obvious when we examine the bond of relationship existing between bodily and mental phenomena. Seeing some one hurt in an accident, or the sight of blood, often causes the observer to vomit or faint; the excitement of joy or anticipation gives rise to loss of appetite and a state of indecision in daily duties leading to indigestion and insomnia; the presence of jovial, cheerful companions at a feast will enable one to consume enormous quantities of food with impunity. Moderate sorrow increases, great sorrow checks the flow of tears; tense anxiety gives rise to cold, clammy skin. The change in quantity and quality of milk in the breast of a mother because of emotional excitement, with consequent injury to the infant, is a common occurrence. When one has not eaten for several hours, the sight of a well-arranged display of pastries or the odor of a busy kitchen will arouse a gnawing hunger and cause a flow of saliva and gastric juice. How often have I seen the medical student, facing an examination, suddenly find himself suffering with nervous diarrhea, a splitting headache, or, as sometimes happens, mental vacuity! Who has not seen the blush of shame or modesty; and what doctor has not observed a patient's pulse rate of 70 rise to over 100 during the first consultation?

Conversely, the various bodily affections influence the mind in various ways. The apathy, mental dulness, hebetude, coma, or delirium, caused by the various toxemias and febrile affections are matters of daily observation. The sudden loss of blood in the brain through peripheral hemorrhage results in vertigo and syncope; an increase in

thyro-adrenal activity gives rise to the alertness, the extreme cerebral hyperactivity characteristic of exophthalmic goiter; a diminution of thyroid secretion is conducive to the slow vocalization and tardy cerebration symptomatic of cretinism or cachexia strumipriva, as the case may be. The drowsiness, fatigue, and sluggishness following the ingestion of large quantities of food, especially meats, is the common experience of almost everyone. What "school marm" has failed to observe the close relationship existing between adenoids and mental deficiency among her pupils? And what busy doctor has not observed an occasional instance of talkative delirium following the instillation of a drop or two of atropin solution into the conjunctival sac?

The physician cannot be a master of the body unless he is also master of the mind, for the two are inseparable. It is not fair to compare the living human body to a boiler or locomotive as is commonly done in our public schools, and often implied even in our colleges. The body is not merely the place where there must be maintained the proper equilibrium between construction and destruction, between anabolism and catabolism. The human being has a mind which profoundly affects the entire body, and this body profoundly affects the mind in return. Man has a thinking apparatus which the machine has not; his feelings can be injured, quickened, depressed, with various bodily reflex results. Man can love and esteem, and, unfortunately, hate, and is ever desirous of being loved and esteemed by his fellows. A disturbance of the balance of man's affections, passions, or feelings is always accompanied by bodily derangements, perceptible or imperceptible; and, contrariwise, bodily derangements, no matter of what nature, influence the central nervous system in varying degree.

THE PHYSICIAN HIMSELF

The physician, realizing this constant relationship between body and mind, must be equipped to correct any maladjustment of this relationship by assisting both body and mind. This requires that he acquire not only a medical education, but a knowledge of normal and morbid humanity bared of its conventional veneer. Moreover, aside from a knowledge of practical psychology, the physician, in order to obtain an advantageous *rapprochement* to his patient, must eliminate his own frailties and foibles and become as nearly as possible equipped to apply himself equally well, with a vivid, strong personality, to all strata of mankind. He must indeed endeavor to speak and understand the language of his patient, whether the latter be a captain of industry, a common laborer, a social outcast, or a society matron. The doctor must rise above all caste and give aid to all on the basis that each human being has a common origin and a common eternity. Withal,

the doctor must be dominated by an unfailing equanimity, as has been stressed by Osler. The disciplined tranquillity of the physician breeds confidence and faith—two things of inestimable importance in the management of subjects of Graves' disease.

In Graves' disease the physician is often obliged to manage his charge in much the same manner as he would a mental case. He must therefore be, in part, a sort of alienist, and as such capable, through proper suggestive influences, of bringing pressure to bear upon the necessary emotional channels with a view to inspiring complete willingness and determination to coöperate, in order to secure as prompt and complete a result as possible. The essential point, then, is implicit, unconditional confidence of the patient in the doctor, since the patient must consider his medical caretaker as his truest friend.

Not only must confidence be won, but care must be exercised to keep it alive and fresh in the patient by the happy countenance and cheerful soothing manner of the doctor, inspiring a feeling in the patient that all is well. A knowledge of current literature, the most important of the classics, and especially an acquaintance with the works of representative humorists will reinforce the armamentarium of the physician to a surprising degree. The physician's wits are often taxed to the utmost, because of the numerous types of temperament or personality with which he is confronted. The jolly and the indifferent, the stupid and the silly, the hypersensitive and the pessimistic, the young and the old, the capitalist and the pauper,—each should find in the physician his true friend. It is the doctor's duty to analyze each mind in order to reveal and bring to the fore the elements that best suit his purpose. As confidence and respect for the doctor increase, and the patient's volition and power of logical reasoning are improved, the favorable relation between doctor and patient must gradually become the instrument of tactful authority and discipline in the interests of permanent recovery. The doctor's equipment should serve as an entering wedge into the inner life of the patient, enabling him to participate in the feelings and emotions of his charge; in short, to feel with and for the sufferer. Few physicians, and these are the eminently successful ones, are born with these qualifications. The great majority of members of the medical profession must acquire this asset sooner or later, if they are to reach a successful goal. Those doctors who fall by the wayside and blend into other pursuits of life, are those whose make-up renders it impossible to adapt itself to these vital requirements. The doctor who is an automatic prescription writer, who merely feels the pulse, observes the temperature, formulates a chemical concoction, then disappears, forgetting to devote at least as much time to the mental as to the physical construction of the patient,—the doctor, in brief, who treats every patient as a "case," without an attempt to lend cheer and delight to his social atmosphere and make the sick

one delight in his presence, lacks at least 50 percent. of the qualifications of his calling.

Aside from intrinsic qualifications already alluded to, the doctor must also possess certain outward qualities in the achievement of the purpose of his calling. Equanimity, poise, and an attitude of cheer and friendship are both intrinsic and extrinsic in nature, and their existence, to do the most good, must be outwardly expressed. The matter of clothes must never be ignored. A multicolored necktie, unpolished shoes, uncreased trousers, absence of laundered cuffs, languid, unshaven features,—all or any one of these may seal a lack of confidence and respect for the doctor. I have seen a patient shrink from one who, though otherwise dressed beyond reproach, was unconscious of the fact that his collar presented a blood stain caused by a slight laceration of the skin through shaving. A medical attendant must be dressed in conservatively up-to-date fashion. He must be neat and immaculately clean. His appearance and poise must bespeak a keen observance of physical and mental hygiene—his features should glow with the joy of life and health,—an example to those whom he is called upon to assist.

THE PATIENT HIMSELF

"Curious odd compounds are these fellow-creatures at whose mercy you will be; full of fads and eccentricities, of whims and fancies; but the more closely we study the little foibles of one sort or another in the inner life which we see, the more surely is the conviction borne in on us of the likeness of their weaknesses to our own. The similarity would be intolerable if a happy egotism did not often render us forgetful of it. Hence the need of an infinite patience and an ever-tender charity toward these fellow-creatures; have they not to exercise the same toward us?"—*Osler*.

The Ego.—In dealing with mind, we deal with the ego, or selfhood. The normal self is the great problem in the study of ethics and its offshoots—sociology, political economy and, in fact, everything involving human motive and action. No one completely reveals himself at any time. "You must eat a peck of salt with a man before you know him." The animal, the primitive man and the child are said to be more consistent in selfhood than the modern human being, as variability of mental action comes with development. How often do we hear the excuse, "I was not myself," or "I lost myself when I did that"; and when the acts calling forth such excuses pass beyond the arbitrary boundary of normality we reach the field of mental aberration commonly expressed by suicidal and homicidal tendencies, hysteria, melancholia, and the like.

Between the dual nature of "Dr. Jekyl and Mr. Hyde" and the

duality of selfhood hardly expressing itself as such there are various gradations. All human beings possess an inner and an outer self—a condition tantamount to dual personality; this is often strikingly emphasized when the inner, unpolished self is revealed in its true color, when volition is suppressed during sleep-talking or when under the influence of alcoholic or other forms of intoxication. Each self—one the nobler, the other the coarser,—possesses a degree of comparative prominence and separation from the other, differing with individuals. We also find that at different times in the lives of individuals, one self, heretofore suppressed, finds ascendancy and expression over the other self, as seen when a criminal becomes a minister, an honest man a thief, a drunkard a model husband and citizen. Inspiration itself, whether religious, patriotic, or esthetic, is the expression of one at the expense of the other self.

Temperament and Disposition as Related to Graves' Disease.—

In the consideration of the mind, we must take into account the basic temperament of the individual. Temperament is a flexible term, capable of varying definitions, but for our purpose it may be defined as that constituent of selfhood indicating by word and deed the usual type of tendency of an individual during ordinary and extraordinary circumstances. Does temperament bear a causal relationship to the production of exophthalmic goiter? We need but recall that this disease is nearly always prevalent in persons whose psychical centers are continuously on the alert, and that this state of alertness reaches its climax in the occurrence of the Graves' syndrome, to respond in the affirmative. The optimistic temperament in which all is song and happiness,—everything in the world from the Deity above, throughout all Nature, even to the very storms and earthquakes, is good,—rarely, if ever, furnishes a case of exophthalmic goiter. The indifferent or "callous" temperament is also practically immune. Here, despite the absence of exuberant spirits, the individual usually lives to a ripe old age, for he is flustered by nothing; that which would worry the average person affects this one like "water on a duck's back." Incidentally, the person with the apparently indifferent temperament is often the most useful to society, for he is capable of cool, logical judgment in the emergencies of life. The stupid temperament, incapable of emotionalism, not because of indifference, but through deficient cerebration, is fairly immune to this disease. The stupid must not be confused with the silly temperament, a state of selfhood in which emotionalism—crying, giggling, depression and exhilaration,—all the various moods may become prominent and alternate with little or no provocation. Among these individuals we expect and do find numerous cases of Graves' disease. But it is among those of a hypersensitive temperament that we find the greatest number of cases. The man or woman in this category is not necessarily of the "silly" type, as there is usu-

ally a basis for the emotional reactions. "Thin-skinned" is the appellation often used as a synonym for the subject of these emotional reactions. The difficulty lies in the tendency of the individual to exaggerate the circumstances giving rise to the emotionalism. This person is suffering under a constant tension, and life to him is a perpetual succession of knocks and bumps. He is over-attentive, and under the magnifying lens of his mental vision a mole hill becomes a mountain, and the circumstances giving rise to the distress are dismissed with great difficulty. The hypersensitive is related to the pessimistic temperament, a state of mind in which all is dark and gloomy, and the world is "going to the dogs." The pessimist and his frequent periods of exaggerated depression often tries the soul of relatives, friends and medical attendants. This class also offers many cases of exophthalmic goiter to the profession. We could thus enumerate many other varieties of temperament and point out the degree of immunity or susceptibility to exophthalmic goiter, as the case may be. Each presents a degree of normality or abnormality when compared to the arbitrary standard of selfhood; each involves a degree of balanced or unbalanced volition, and many, if carried to the extreme degree, lead, among other terminal states, to exophthalmic goiter or Graves' disease.

If the "normal" person's ego or selfhood presents no fixed character and is often a puzzle to the observer so that allowances must be made by those about him, how much more allowance must be made in the interest of the sick one who is far more prone to variations! It is for this reason that the subject of exophthalmic goiter at times deems himself a martyr to what he considers the antagonistic forces of his household,—the refusal of those about him to make the necessary allowances. Allowances within reason should be made; adjustment of his environments must be effected until the patient is in course of time made to realize that this state of antagonism is largely of his own creation,—that the world is what he makes it,—that it is indeed a good place to live in if he would but coöperate to make it so.

Sympathy and Affection.—An analysis of the case of the "martyr" usually discloses a tale of lack or absence of sympathy of the world at large with his complaints. Although this mortal is surrounded by relatives and friends, he is alone—intolerably lonesome, as one on a desert isle. He is yearning for someone to whom he may impart his suffering,—someone whom he may trust, to share in his misery. It is in this state of mind that the gregarious instinct,—the basis of individual and social self-preservation, asserts itself most prominently.

Dubois has well said that "we physicians ought to show our patients such a lively and all-enveloping sympathy that it would be really very ungracious of them not to get well." The common mode of treating neurasthenia, hysteria, the hysteroid and other forms of emotionalism commonly seen in exophthalmic goiter (from the ranks of which these

"martyrs" arise) has been by icy sternness. "Do not sympathize with her; she must be forced into common sense. There's nothing wrong with her; she's just bluffing!" These and similar exhortations have been the doctor's orders with respect to these unfortunate creatures. Could you quench fire with more flames, and calm an excited mob by inciting more anger? If these are impossible, so is it the height of folly, so is it cruel and inhuman further to rouse the turbulent emotions by antagonism. Efforts at logical subjugation of the patient to common sense, and at persuasion, with a view to the avoidance of further outbursts of these "fits," should be tried with intelligence, caution, and tact, and only between attacks, i.e., during the intervals in which there is relatively good health, or after the patient has been sufficiently nursed back to health to be capable of calm, deliberate reflection. The nervous patients, not only women, but men too, demand not severity and frigidity of the caretakers, but the kindest charity in the method of approach, for these poor souls suffer most of all from *love starvation*. Such a patient's doctor, nurse, and relatives must exercise temperate judgment, patient firmness, discretion in word and deed, and an earnestness which wins the confidence of the weak one. The latter, fed on this sympathy, affection, love, soon ceases to be starved; there is a restoration of emotional stability, strength of mind and body gradually returns, and in time the patient is well and strong.

It is admitted that many of these patients are unreasonable and at times exasperating. But is not this person suffering from an abnormality? If this be so, why not treat by the neutralizing, the mollifying forces of mental therapy? In fever we sponge the patient, administer cold beverages to quench thirst, overcome respiratory embarrassment by plenty of fresh air, apply an ice bag to soothe an area of congestion. Then is it not reasonable, humane, and the most natural thing to combat a mortal's mental turbulence by the calm, soothing, healing influence of sympathy and affection?

Confession.—In this connection, it must be observed that the patient's habits, tendencies, and petty obsessions and vices, if these exist, must be learned. Often, after confidence is secured, he or she will confide in the physician the secrets which have been torturing the mind, and which have been the cause of the difficulties. How often is it discovered that the trouble began with lack of affection on the part of one or more relatives or friends! How often is it the old, old story of unrequited love of the opposite sex! A confession is then a rather fortunate circumstance, for there is not only a relief of the marked mental tension, but, what is most valuable, it gives the physician an opportunity immediately to endeavor to overcome the cause of the trouble by the proper psychical appeal. To quote our esteemed Weir Mitchell: "To confess is for some mysterious reason most profoundly human, and in weak and nervous women, this tendency is sometimes

exaggerated to the actual distortion of facts. The priest hears the crime or folly of the hour, but to the physician is oftener told the long, sad tales of a whole life, its far-away mistakes, its failures, and its faults. The causes of breakdowns and nervous disaster, and consequent emotional disturbances and their bitter fruit, are oftener to be sought in the remote past. He may dislike the quest, but he cannot avoid it. The moral world of the sick-bed explains in a measure some of the things that are strange in daily life, and the man who does not know sick women does not know women."

Tact in Sympathy.—What is that which I call sympathy? It is a quality which enables one to enter dramatically into the joys and sorrows of others, to comprehend what others suffer and experience. In brief, to feel with and for the sufferer, and to be able to assist in calming the troubled waters of life by proper word and deed. Though this quality is most easily acquired by those who have themselves suffered, this is not necessarily the case. Many physicians who have not suffered greatly in body and mind, but who are endowed with a benevolent, imaginative power, feel for and with their patients, even to the extent of actual subjective suffering. Here let me sound a note of warning. As in the case of drug administration, the patient has his or her idiosyncrasies, comes from this or that social, intellectual or financial stratum, is subject to various mental peculiarities, and consequently requires careful study before actual mental therapeusis is attempted. Strict individualization is therefore the keynote in this regard. The mere poulticing of the feelings of the sufferer through a few ingratiating, stereotyped phrases, may do for the average mortal or for the weak-minded creature who is so sympathy hungry as to reach for even a tiny crumb of affection; but the patient possessing active reflective powers secretly rebels against the doctor who lacks tact and diplomacy. Real sympathy can only be meted out by the student of human nature capable of individualization; each case is quite different from all the rest; the doctor's words and actions must reveal in him a keen interest, a strength of purpose, originating from firmness of conviction and from self-confidence, which alone can gain respect.

Indulgence.—While an oversupply of sympathy, affection, and indulgence in the petty whims of the patient is possible and even desirable for a time, a continuance of this is not advocated when the patient is obviously improved and volition approaches the normal. When a definite state of convalescence is reached, all the suggestive powers of the medical attendant must be brought to bear in an effort to have the patient think along logical lines. Success attends these efforts in the vast majority of cases if the physician adopts the proper mode of procedure by employing the necessary tact and diplomacy. The members of the household, especially the fond helpmeet or parent,

must be instructed to coöperate in this matter. It must be firmly stated that sternness in obedience to orders shall and must characterize the treatment, and the physician must take the trouble to elucidate clearly the reasons for his stand. Regularity of sleep, rest, exercise, feeding, proper attention to bathing, the quality and quantity of foods and beverages, the kind of recreation to be indulged in,—each and all must be given careful attention, lest the patient step back from a greatly improved state to his former miserable condition. To become the least bit slipshod or indifferent to the strict regimen outlined by the physician is to play with fire and invite a serious if not fatal relapse.

The Love Problem.—The term "love" may indicate an intensified degree of affection for another individual, irrespective of sex, or it may imply an attraction for the opposite sex and a craving for sexual gratification. Whether we should consider the one pure and the other impure depends largely upon circumstances and the relationship of those concerned; this I shall leave for the moralists to decide.

Many a nervous individual, whether hysterical, neurasthenic, or a subject of Graves' disease, will, when closely questioned, reveal a state of what I term *love starvation* as the starting point of the disease. Lonesome maids and bachelors living in almost total solitude are instances of this sort. The lack or deficiency of parental affection will often cause the child to become morose; an old mother will become melancholy on seeing her adult son or daughter drift away from maternal ties. Brothers, sisters, cousins, all are now and then, consciously or unconsciously, guilty of misapplication or withdrawal of the love which they are bound by blood ties to manifest, and the sufferer finds herself or himself in the doctor's office, a subject of nervousness. The sudden frigidity of friends, inconsideration of employers, an occasional slur through word or deed by an acquaintance, the boarding-house mistress, or even a stranger, will in some cases be the starting point of a spell of nervousness leading to hysteria. The human being is essentially the mind; the body is quite similar to that of the lower forms of life. This mind is in its very selfishness possessed of gregarious or social cravings; in other words, the human mind yearns and lives for affection, esteem and love of those about. There is no such thing as a real hermit. This love-craving propensity is adjusted with a fine, hairspring mechanism, so that a slight glance, a word, a gesture, results in anguish, self-torture and emotional outbursts.

Sexual Problems.—But by far the most important phase of the subject is that dealing directly with the sexual life of the patient. Here the term love (as emphasized by Freud) bears directly on a consideration of the sexual instinct. If the sexual life of each nervous patient seen by the doctor on his rounds were inquired into, what interesting information would be obtained! What a vast world of hidden disappointments, embarrassments, tortures, mortification, and degrada-

tion would be revealed if strict candor were observed in these histories! And, to revert back to the subject of Graves' disease, how often have I seen advanced cases of this sort whose etiology may be traced back to disturbed sexual balance! Is it not obvious that if the sexual instinct can give rise to the most intense emotions, the resulting disturbance of the mental life may lead to neuro-endoerine imbalance, and since the physiology of the endocrines and the vegetative nervous system is so intimately related to the sexual make-up, its function would be the most susceptible to derangement?

Concrete examples of this state of affairs are numerous. Take the case of a young woman with advanced exophthalmic goiter of two years' duration. She has been engaged to be married for some years prior to the onset of the disease. In the absence of other etiologic factors, what is the inference? Prolonged engagements, with their late hours and other features which we leave to the reader's imagination, are decidedly inimical to physical and mental stability. A case of this sort requires extreme tact and firmness; the lovers may be permitted to see each other once a week for an hour or two in the presence of the household. A six months' careful treatment may result in such improvement that the couple may be permitted to marry. The young woman should be kept under observation for six months or a year longer, until the cure is effected. During this time the necessary sexual instructions should be given both husband and wife, among which must be included the use of separate sleeping chambers.

We often see an instance resulting from excessive sexual indulgence with its perpetual congestion of the pelvic organs, extreme nervous tension, and dread of the unreasonable demands of the husband. Or the wife may be a subject of frigidity even in the presence of normal demands, and the dread of the husband's advances may have brought about her condition. Here the medical attendant should have a heart-to-heart talk with both parties and carefully but fully explain the situation without mincing words. The treatment, to be successful, must include a serious attempt at sexual equilibrium. To this end both husband and wife must be treated as the exigencies of the case demand.

Here we have an instance of vaginismus or of priapism, as the case may be; there, a case of marital maladjustment because of malformation of the sexual organs; now, a serious case of prolonged masturbation; again, a patient suffering with venereal disease or pelvic neoplasm. In each of these and in many other sexual affections which could be cited as bearing a causal relationship to endocrine dysfunction, the attempt at restoration of normal structure and function may require the assistance of a competent gynecologist or genito-urinary specialist, as the case warrants.

These cases offer great difficulties, as in the usual instance the mention of sexual matters, especially if the patient be a female, renders

her loathe to talk freely. It must be explained to the patient that sexual organs are attributes of normality, and that it is just as proper to discuss with the doctor the organs of procreation as to discourse on the organs of digestion or respiration. It must be further explained that legitimate sexual intercourse is a moral act, an act sanctioned by God and Nature in the interests of race preservation. Thus the degree of false modesty is usually removed and a state of mutual confidence established. The medical attendant who knows human nature well will have little difficulty in completely revealing a sexual history which might prove of inestimable value in the interests of prompt recovery.

Social Adjustment.—The matter of the relation of the patient with the prevailing social environment has already been alluded to in the foregoing remarks and in the chapter on guiding principles in treatment. We shall here add a few factors requiring the attention of the psychotherapist. The patient's household is often the place of antagonism to the favorable course of events in treatment. Whether it be husband, wife, son, daughter, or other relatives, the close association, instead of enhancing contentment, concord and happiness, may breed contempt and chronic uneasiness, most often, of the ailing one,—a disgust of the strong for the complaints and foibles of the weak. Thus the patient becomes a victim of social environments. Here also the doctor's duty is one replete with tactful authority and stern appeal to those of the household for hearty coöperation. He must take them into his confidence and explain that "a house divided against itself cannot stand." He must point out that though all members of a family are not of the same temperament or disposition, the properly regulated household should not only seek to avoid conflict on the issues of disagreement, but must deem it a duty to arrange for frequent moments of happy reunion. Certain hours during the week should be devoted to mutual entertainment, games, music, reading and the like, so that the family as one person may enjoy itself in a harmony that spells health and life to all. It should be emphasized that each member of the family, but especially the ailing one, should have not a house, but a home to live in.

Often the household is just what is lacking, the subject being a maid or bachelor without friends, suffering with the oppression of loneliness and solitude. Here the physician's task is difficult, and his mode of procedure will depend upon the nature of the individual circumstances—the patient's personality, economic resources, and the severity of the disease, with a view to advising a change of social environment. Marriage, as soon as circumstances become favorable, is the ideal change.

Occasionally a patient's difficulties are in the form of acquaintances who, as bores or tactless diverters of mental health, consciously or unconsciously play the part of antagonists who hinder recovery. It

is often difficult to discover and weed out these undesirables, but sooner or later this is accomplished, again by tactful firmness, so that no one need be offended. It should be made known to those whose company is harmful that visitors are prohibited. False and undiplomatic visitors are not only in the way, but at times bear an etiologic relationship to the incidence of the patient's affection. At the same time a few of those whose presence is a help may be permitted about the patient, to keep him from becoming lonesome.

Work.—Patients whose economical resources are meager and who must work for a living, seem to offer a serious problem for solution, but in reality this is not so in the usual case. Most often the wage-earner will improve more rapidly than the idler, simply because the former has very little time to become self-centered. Psychotherapy here has little to do excepting the maintenance of a state of cheerfulness and the instillation of confidence in the future. The place of employment (assuming that the patient is strong enough to work) must be such as to offer no serious criticism in the interests of physical and mental health, and if favorable conditions do not obtain, a change must be made. Long hours, excessive physical and mental strain, poor ventilating, lighting and heating systems, dust and other impurities in the atmosphere, and last, but not least, uncongenial co-workers and exacting employers,—all these must be taken into account and avoided.

Idleness.—Often the difficulty is just the reverse from the foregoing. Instead of too much work, there is nothing at all to occupy the patient's mind, excepting the doting on signs, symptoms, and the prognosis of the disease. Continuous idleness may cause more harm than a nine or ten hour day's work. In other words, complete physical rest is in most cases productive of an "overtime" state of nervous turbulence. Excepting in the event of extreme tachycardia or an organic heart lesion, complete idleness should be guarded against as inimical to the favorable course of events. The patient's mind must be occupied during several hours daily with some vocation or avocation of an interesting nature. A state of idleness in bed for many weeks is often enforced upon the patient by the attending physician with the view of "resting the heart." Innumerable instances of exophthalmic goiter treated in this way have led to the conclusion that a heart without organic lesions is not rested by this means. A prolonged rest in bed is not rest at all, but a means of increasing the state of physical and mental irritability. The question of rest and exercise is further discussed in the section on hygienic treatment of exophthalmic goiter.

Sleep and Dreams.—Directly related to the matter of work and rest is the subject of physiological unconsciousness, *sleep*. Unless the third of our lifetime devoted to bed is productive of restful rejuvenating sleep, *without nightmares*, mental and physical deterioration is bound

to ensue. Subjects of Graves' disease are almost constant sufferers from the most stubborn devitalizing insomnia, which causes an indescribable sense of wretchedness on arising. All reasonable efforts must be made toward the attainment of sound, refreshing sleep, a most potent ally in efforts to restore our patient to a satisfactory mental and physical adjustment. This subject has been discussed in the chapter on the nervous symptoms in Graves' disease.

Religion.—Bearing upon the topic of the unconscious and subconscious of sleep and dreams is the question of religion, which occupies an important place in the subconsciousness of every individual. The matter of religion applies both to physician and patient. An atheistic medical attendant never succeeds as a psychotherapist, and an atheistic patient is a poor charge. The instinct of self-preservation, to be healthy, requires also a healthy religious viewpoint to sustain it. Spence aptly points out that on analysis, despite asserted antagonism, rational thinking and religious belief are interdependent. Whence do we come, and whither bound? are questions in the minds of all who think, and uppermost in the minds of many overly alert individuals with Graves' disease. I have often tested this out by intimate conversations with patients, and have discovered that, aside from being really religious, many go beyond the bounds expected of them by the Deity and are suffering with religious fantasies and obsessions. It is the duty of the physician to train the mental trends of the patient in order that a healthy philosophy of life be attained,—a rational faith in God and man, a belief that all is well and will continue to be well here and hereafter. The calmness and serenity of mind, the surrender of the emotions to a healthy Faith, is a potent weapon against mental disability upon which much of the physical ills of mankind depend.

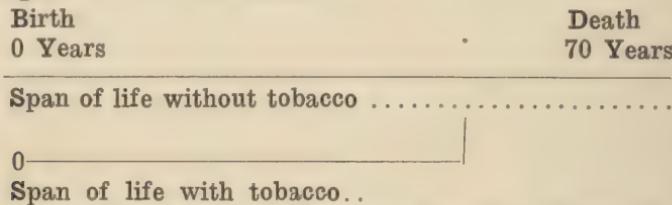
MORE DIRECT METHODS OF PSYCHOTHERAPY IN EXOPHTHALMIC GOITER

We have already discussed in general some of the tasks of psychotherapy in Graves' disease. The duty is twofold: (a) The elimination of erroneous and harmful mental habits, and (b) the inculcation of habits which tend to give the patient the most satisfactory adjustment between himself and the world at large, and so reflexly to enhance a state of physical health and usefulness.

Elimination of Emotionalism.—To repeat what has been mentioned in the chapter on symptomatology, the extremely lowered threshold of emotional reaction is a prominent phase of the nervous manifestations of these patients. Emotionalism is a constant phenomenon in this disease, and the patient is aware of it but is powerless to control it. The spells of crying, resentment, moodiness, melancholy, anger, and even giggling, must be curtailed and kept under the control of reason in much the same manner as it is done in a child, by tact, conviction,

persuasion and training. Once the medical attendant has the confidence of his patient, no obstacles are encountered in the task. Fortunately, the disappearance of emotionalism is one of the earliest evidences of a successfully applied régime of treatment, and need not give the medical attendant much concern.

The Tobacco, Coffee, and Other Habits.—These have already been discussed in the chapters on the prevention of exophthalmic goiter, on the diet, and elsewhere. We need only repeat that the medical attendant must have complete control over the patient in the elimination of faulty dietary and related habits. If, after several earnest appeals, the physician discovers that the patient is untruthful and otherwise deceptive, taking plenty of tobacco, coffee, meats, and other forbidden substances, it is better to discharge him without further ado than to court failure in treatment. The tobacco habit is the most difficult to eradicate, but the following device has yielded excellent results. The patient is given a brief talk on the obstacle of tobacco to treatment, and a diagram is drawn as follows:



In explanation of the diagram I usually say, "My friend, our span of life, without poisons, should be a minimum of three score and ten—the distance in years between birth and death. With poisons, and tobacco, by virtue of its nicotine, is a potent poison,—you cut off a goodly portion of your allotted existence. Life, you will admit, is the most precious thing in thought. Would you rather take tobacco than live? Again, life with tobacco is not 'a short life but a sweet one,' but its very brevity is due to its bitterness,—the impaired health from the saturation of the body with poison. It is the long life that is sweet, because the long life is unimpeded by the diseases due to poisons. Take your choice, then, between a short life and a bitter one, and a long life and a sweet one. Is tobacco worth while? I want you to promise that you will never use tobacco again!" The force of the argument is irresistible, and instead of saying "I'll try," or "I'll take less" the patient, enthused by the interest taken in his health and life, promises by saying, "I shall never use tobacco again!" and that settles the tobacco question in 49 out of 50 patients.

Monotony, Hobbies, and Recreation.—Introspection and other unhealthy mental habits are frequently kept alive by a surplus monotony in life and a deficiency or absence of hobbies and recreation. Early in the management of Graves' disease the establishment of the neces-

sary equilibrium between duty and pleasure, the serious and the light, vocation and avocation, must be attempted with a view not only to immediate, but to perpetual benefit. How to accomplish this depends upon the many factors pertaining to age, sex, intellect, social stratum, and other conditions of the life of the patient. In this age of comfort and recreation a hobby or form of amusement can be found for each type of patient without difficulty. Hobbies to overcome monotony are so numerous that they need not be mentioned. Recreation, however, requires considerable guidance, since much harm can accrue in impressionable patients from wrongly selected means of diversion.

Music is by far the most useful form of recreation, and may serve in a way as an excellent hobby. The influence of music on the nervous system is undoubtedly due to the frequency, altitude, and especially the rhythm of the sound waves. All Nature is motion, and all motion is rhythmical in character. Rhythm is a fundamental law of progression and metamorphosis. Music is salutary because its sound waves consist of regular, even, rhythmical vibration, which favorably influences the higher nervous centers, and, reflexly, the various organs through the sympathetic nervous system, thus improving appetite, digestion, assimilation and nutrition. Properly selected music may be advantageously employed as a supplement to other therapeutic measures in all conditions in which the nervous system is largely implicated. As disease is really a departure from the proper rhythm of molecular changes of cellular structure, music, insinuating its order and rhythm upon arrhythmical biological processes, is a potent accessory factor in the armamentarium of the psychotherapist. This has been recognized of late years in clinics throughout the world, as evidenced by the institution of music clinics for nervous affections in sanatoriums in France, Germany, and elsewhere.

Music can sway all living things endowed with a central nervous system. The more highly organized the nervous system, the more profound this influence, until in man, music becomes the physic for the soul, raising it above the gross reality of tangible trials and tribulations, leading the subject on to vistas of superstructural formation, not unlike a pleasant dream state. Music under such conditions fills the niche to complete the regimen of treatment outlined by the medical attendant, and is often the means of entering most deeply into the mental life of the patient when other measures fall short of their purpose.

Music seems to have a special predilection for the will of the listener, overcoming stubbornness, and substituting an ability to reason logically to an extent equalled only by the effects of a powerful sermon. As the will of the subject of exophthalmic goiter is often capricious beyond reason, music, although the most severely abstract of arts, is often capable, through its very subtlety of speech, of giving support

and rationality to the stream of consciousness, and serves to improve the moral backbone of the patient in question.

It is to be remembered that here also individualization is essential. Music must be prescribed with reference to its quality, quantity and duration, the idiosyncrasies of the patient, and the prevailing environments. Some kinds of music exert a universal influence over the audience, which, as one man, is carried away in an ecstatic dream to Utopian lands and the realization of cherished hopes; the grossness of earth's reality, its knocks and pains, are effaced; the listener loves the present, and looks forward with extreme joy to future possibilities and glorious accomplishments. Such is possibly the effect of Beethoven's "Fifth Symphony" and some parts of his "Moonlight Sonata." Other compositions differ in physiological effect. Schubert's "Unfinished Symphony" exerts the pleasurable effect of a somnolent state, not unlike the influence of a moderate dose of morphin. The same may be said of Schubert's famous "Serenade," although this leaves, in addition, a tinge of sadness. Wagner's music, especially the "Pilgrim's Chorus" from "Tannhäuser," is most often a potent stimulant, raising the spirits from their haven of helplessness to fill the patient with firm determination to do and win. But some compositions, on the other hand, may do a little harm. Drigo's "Harlequin's Serenade," though an infinitely beautiful selection, will cause weak-minded individuals a degree of sadness which may lead to tears. The same, to a lesser degree, may be said of Massenet's "Elégie." While occasionally a "good cry" results in beneficial reaction, we must in general seek to produce not tears, but smiles of contentment in our musical program. Moreover, not all our patients are capable of appreciating the classics. Some grow impatient with the slow, steady progress of a theme, such as occurs in Beethoven's works; others are totally devoid of this form of esthetic appreciation; still others have decisive inclinations for such conglomerations of notes found under the heading of "jazz"—the prototype in sound of "cubism" in art. Shall we deprive these mortals of the pleasure of the popular ballad, dance music, and even "jazz"? Decidedly not, if this is seen to assist recovery. The patient who is unappreciative of the classic has just as much right to his standard as the cultured individual has to his, and we must admit that it is really difficult to prove which standard has the greater right to exist.

Music has a place in the nonsurgical management of exophthalmic goiter. Although most patients, perhaps we should say all patients, can get along without music, we must not omit this form of mental treatment when it is available. The tachycardia, the emotional excitation, the general nervousness, and the various functions of the body which are in a state of overactivity are held in abeyance, and the greater the susceptibility of the patient to music, the more grateful the effects. Though the effects, to be sure, are evanescent in character, the frequent

administration of the necessary dosage and quality of this remedial agent will, as in the case of most drugs, create an overlapping and accumulation of results so that sooner or later with influences exerted by other measures employed, permanence of results is attained.

Reading, Lectures, and Conversation are likewise useful in dispelling monotony and disengaging the mind from introspection. Here, too, individualization must be exercised. The patient may be permitted to read, or he may listen to someone else whose voice and interpretation may furnish pleasure and mental repose. Because of the condition of the eyes and nervous system, the patient should never be permitted to read small print, or in an improper light or position, or for too long a time.

Representation in reading is capable of calling forth nearly every emotion—stimulation, depression, smiles, sympathy, scorn, and the like, as well as the feeling of esthetic delight experienced from music and art. It is for this reason that a careful selection should be made by the medical attendant of the reading matter to be permitted the patient. Newspapers should be prohibited, as their contents are often too markedly depressing for one whose emotions are overalert. Mystery stories, tragedies, talks involving extreme suspense, and the like, should also be forbidden. Reading matter should be of light, wholesome, cheerful character—clean and refreshing throughout. We cannot recommend too highly certain delightfully humorous selections as represented by the "Pickwick Papers" by Dickens; "Tartarin of Tarascon" by Daudet; nearly all of the works of Mark Twain and of Jerome K. Jerome, especially "Three Men in a Boat" by the latter; "The Laughing Muse" by Guiterman; and for those who are fond of Shakespeare, such plays as "The Comedy of Errors," "Twelfth Night," and "The Taming of the Shrew." Some subjects, however, find themselves in the best mood when reading the modern short story of romantic or witty trend as found in the short story magazine. In addition to those mentioned, I find that among contemporary authors the semi-philosophical works of H. G. Wells and Arnold Bennett and the humorous writings of P. G. Wodehouse and H. C. Witwer are very useful.

During recuperation of the patient other forms of diversion may be added. Attendance at lectures and sermons with or without screen illustrations may be permitted at the discretion of the medical attendant, and they are subject to the same remarks as those which cover the question of reading. The topic must be of a cheerful, inspiring, elevating type, and must not be capable of fatiguing the listener.

Conversation, especially table talk, is a consideration of importance. Those participating in it should be instructed to speak in a soft tone of voice, never to jar the patient's nerves by violent gestures and phrases, and above all, to discuss only those topics which would not arouse and excite the emotions. The narration of a funny incident and the recitation of a humorous selection are always in place. As these patients

are usually of hypersensitive nature, they should be permitted to participate not only as good listeners, but should be encouraged actively to take part in agreeable conversation in order to forget themselves. The duration of the conversation should always be taken into account.

Attendance at the theatre may be permitted with due regard to conditions and circumstances herein implied.

Radio entertainment in the form of lectures, plays and music offers enjoyable diversion for the least outlay of expense and energy, and enables the patient to keep in touch with choice current events without recourse to the newspaper. As a factor in overcoming introspection such entertainment is one of the best means at our disposal.

Miscellaneous Esthetic Recreation.—Among other esthetic pleasures which appeal to the emotions and favorably influence their balance are an occasional visit to an art gallery, a trip to some lovely country spot for the contemplation of Nature's beauties, or even an occasional leisurely trip through the large city stores, that the eye may note and admire the modern wonders of man's handicraft in clothes, ornamentation, and the like. Here we obtain through the visual apparatus what music offers through the sense of hearing—a primary central thrill of pleasure with a secondary reflex reverberation in the various organs of the body. These trips should be taken only after a sufficient degree of recovery is attained.

Lastly, we must not overlook the spirit of optimism and smiles which should permeate all psychotherapeutic efforts.

Smiles and Laughter.—He who smiles wins. This applies to both doctor and patient. That a sense of humor is quite compatible with dignity is conspicuously illustrated by Abraham Lincoln whose funny anecdotes were largely instrumental in making him the power that he was.

A very popular Philadelphia physician once told me that the secret of his eminent success lay in getting all the wholesome fun he could out of practice. This disciple of Hippocrates—a picture of health—tall, robust, eyes ever gleaming with joviality, would no sooner enter the sickroom when the eyes of the patient would brighten, a smile would soon efface the lines of suffering, and within a minute or two both doctor and patient could be heard laughing in carefree abandon over some funny story which served the purpose of the time. The doctor was up to the minute on the literature of the day, could discourse with rare intelligence on the merits of contemporary authors, and above all, possessed an enviable stock of funny stories and jokes, which, though not included in the *materia medica*, often far surpassed it in therapeutic efficacy. While an excellent physician, this man, in "getting fun out of practice," had secured more friends than any two ultra-scientific doctors I have ever known.

Laughter is more contagious than measles, and, in possessing no rash,

is infinitely more useful. Laughter loves company and is therefore a powerful cementer of social ties. "Laugh and the world laughs with you" is a truism worthy of deeper contemplation. The world not only laughs with you, but the world wants to know you, to love you, if you but laugh. The world laughs with you not because your laugh is the result of something extremely witty, humorous, or ludicrous, but because the world loves to laugh for the sake of laughing—because laughing is a pleasurable act giving rise to a state of agreeableness of body and mind. Need we insist that laughter dispels gloom, inspires optimism, imbues the spirits with the joy of life? Need we recall that laughter increases appetite, improves digestion and assimilation, favors healthful, refreshing sleep, and improves physical and mental usefulness? And wholesome laughter, being an expression of love of fellow-creatures—does it not radiate fraternity—a fellowship tending to diminish worldly discord and enhance the unification of the human family?

The subject of exophthalmic goiter is the picture of perpetual gloom, fear, introspection, melancholy, and other mental states far removed from the glow of gladness. Since laughter is gladness and gladness is conducive to well-being, laughter is a great tissue builder, so that "laugh and grow fat" is not a mere aphorism. In exophthalmic goiter, the sooner the fattening begins, the more prompt the cure.

The medical attendant must himself be the picture of joviality and optimism in the presence of a case of exophthalmic goiter, if he is to impart gladness and smiles to his charge. The serenity of the doctor's countenance must not amount to or be capable of being interpreted into terms of cold, scientific curiosity and indifference to the subjective history and complaints. He should appear serene, but it should be a smiling serenity, a faee of hope "writ large." The patient has gone the rounds and seen many doctors before; operations have been suggested —perhaps she has already submitted to one, perchance to two surgical procedures, and she is not only in a state of exaggerated physical and mental depression, but has lost confidence in medical men as a whole. Someone has sent her to you as a last resort. At first she refuses to go, preferring to live it out to the end. But she is finally prevailed upon to see you, and here she is, a frail, helpless, hopeless, trembling, throbbing creature, her bulging eyes bespeaking a defiance against your potentiality to assist. She happens to be a girl of eighteen, accompanied by her father. You discuss the weather for a moment and smiling sympathetically, you ask her to tell you her complaints. As you patiently listen, you jot down the salient features of her narration and turn to her parent for further history. Then, with soft, modulated voice, you question patient and father until the history is complete, always guarding against overburdening the sufferer with too rapid questioning. Then, as a parent tenderly undertaking the care of a child, the necessary physical examination is made. By this time the patient

begins to feel at home in your presence—nay, more than at home. There is something about your every word and move that inspires that of which she has great need—confidence. She feels that she has reached a medical man who wants to help her, and when you smilingly ask her if she will coöperate in the measures you outline, assuring her of the great prospects of recovery, she promises, almost with enthusiasm. After you have given them the necessary instructions, you cheerfully bid patient and parent a warm *au revoir*, and with fatherly handshake inform them when to call again. One week, two, three weeks pass by, and your patient begins to improve in every respect. At the termination of a month, although she has gained 8 pounds in weight and appears and feels better, she is still morose and melancholy, and you feel that a cheerful attitude would mean more rapid progress. This time, when she appears with her father in your office, you are determined that smiles must predominate. "My child," you say, "you are getting better, aren't you?" "Yes, but I am not quite well yet. I still have some diarrhea, and I don't weigh quite enough, and I get weak when I begin to do anything." "Hold on a minute," you interpose. "You have been an invalid for nearly two years—do you expect to get well in a month?" "No, I suppose not," she answers moodily, "but I can't get along with my sisters at home—they annoy me; and I get crying spells and can't eat." "Now look here," you say kindly but firmly, looking straight into her eyes, "if you do not turn the corners of your mouth upward into a smile, I shall refuse to treat you any longer." "Oh, doctor, don't say that!" she exclaims, somewhat startled. "I mean what I say," you insist. "If I cannot get your help to cure you, I shall give you up. I want to convert you from a very sick girl to a well little friend, and all that is now lacking is smiles and laughter." Your face broadens out into laughter as you say: "Now come close to my desk, both of you—father and daughter—and see what I mean." On a prescription blank you draw this diagram:



"This is what you look like, Helen," you say; "now, when you leave this office and forevermore, you must look like this!" You draw this diagram alongside the other:

Helen begins to giggle, then laugh, the first real change of countenance in two years. "Now, Helen, take these along, and spend an hour a day drawing these faces to show me what a wonderful artist you can be!" Father and daughter depart in jovial mood. The patient thrives rapidly, and within eight months you discharge her strong, well, happy, better in every way than she had ever been before, and your lifelong friend. On the day when you discharge Helen, her father takes you aside and whispers into your ear: "Do you know, doctor, she is the most amiable child in the family,—and you should see her eat! Also it may interest you to



know that she is still drawing those faces and teaching everyone else the art. She is especially fond of this one." He takes a piece of paper out of his pocket to illustrate his remark, and it discloses the diagram expressing Helen's present mood:



A young man of 24 with rather severe Graves' disease of 3 years' duration progressed satisfactorily during the first month of treatment, when, after a gain of 10 pounds in weight and corresponding improvement in other respects, further progress became tardy. A friendly chat with him revealed the fact that his home, where he lived with his parents and brothers, was a veritable inferno seething with antagonisms and quarrels. Efforts to correct the household atmosphere failing, I again took the young man in hand and employed this device: "Fred," said I, "your folks at home do not show good sense. Now *you* must prove to be the wisest in the family. It requires two to make a quarrel, and if you do not participate there is no quarrel. Did you ever see the Japanese motto illustrated by three little monkeys sitting on the branch of a tree? One has his hands over his eyes, which indicates: 'See no evil.' The other has his hands over his ears indicating, 'Hear no evil.' The third is even wiser—he holds his hands over his mouth which means: 'Speak no evil.' The combined logic of the three little monkeys—see no evil, hear no evil, and speak no evil,—will stop all strife between you and your brothers, and you will promptly get well. When you see or hear anything which means friction, turn about, smile to yourself and say, 'I haven't seen it—I haven't heard it. I am blind, deaf and dumb!' Simply do this without trying, laugh and your troubles are over." The patient, rather keen minded, understood perfectly, and from then on all was well. Recovery was perfect and complete, and the household, I am informed, is entirely transformed into one of fraternal happiness and concord.

CONCLUSIONS ON PSYCHOTHERAPY

An analysis of the foregoing remarks on psychotherapy will lead to the conclusion that the *modus operandi* of mental adjustment is suggestion, in which an ill mind is assisted toward a healthy status, and through this mental health other measures directed toward *physical* health are eminently successful.

A suggestion is an idea capable of suppressing or engendering another idea. All human life is permeated with suggestion: social existence, polities, business, the arts and sciences, and religion. Generally speak-

ing, the greater the amount of education of the individual or the greater the amount of native mental stability in a patient, the less susceptible he is to suggestion. On the contrary, the lesser the degree of worldly knowledge and inherent common sense, the more likely the subject is to respond promptly to suggestive influences. Patients also differ in accordance with the kind of temperament characterizing their make-up, the presence or absence of morbid obsessions, and the mood at the time suggestive influences are attempted. Also, fatigue, the possible influence of stimulating or depressing drugs at the time of the seance, and even the prevailing weather must be taken into account.

Suggestion is really a process of filling the subject's mind with strong motives to impel action favorable to the attainment of the desired goal. These motives are seven in number: self-preservation, which is recognized as the first law of nature; property, which is akin to the instinct of acquisitiveness; power, or the keen desire to sway others; reputation, where the patient acts in accordance with suggestion because it will maintain his good name; sentiment, affection and taste. The patient's dearest desires and cherished hopes must be discovered, and there must also be a revelation of the most telling weak and strong points of the mental construction. Conviction and persuasion are potent instruments in the attainment of forceful suggestive influences. The patient must be put in a state of mind in which he is convinced that there is something good to live for, and must be persuaded to begin *now* so to think and act that this awaiting good shall be forthcoming as quickly as possible. The most unreasonable and fractious patient possesses some good deeply rooted in his inner self; this must be ferreted out and employed as a root in the development of a healthy mental existence.

The patient with exophthalmic goiter is at odds, so to speak, not only with himself, but frequently with his whole universe as well. For this reason, the physician often finds it difficult to hold his case for a time sufficiently long to enable him to bring about a satisfactory state of rationality. Not a small percentage of cases present this problem during the transitional period, *i.e.*, between the first consultation with the subject and the occurrence of results evident in and to the patient. Even in the presence of the remarkably adequate personality of the physician, and indeed even after the beginning of apparent improvement, a slight relapse in the patient's mental status may lose him to the medical attendant. It can readily be seen, then, that psychotherapeutic measures must at first include an effort to obtain as near as possible a state of equilibrium or harmony between patient and doctor in order that this dangerous transition period be overcome.

In conclusion, we may state that in cases of Graves' disease with accentuated mental symptoms, requiring energetic psychotherapeutic measures, the doctor's task is not an enviable one, but fraught with stubborn obstacles, tedious trials and a continuous vigilance. The

results obtained, however, more than compensate for the pains expended. The physician who undertakes the management of a sufferer from Graves' disease must be master of the situation. He must dominate, by an irresistible magnetism and forceful persuasion, not only the patient, but those about—including husband, wife, parents or friends, as the case may be. He must also aim to make recovery permanent and complete so that health, usefulness and happiness may extend into the future life of his charge.

Having discussed the various measures to be employed in our efforts to restore the subject of Graves' disease to health and usefulness, we shall in the next chapter see how the patient progresses toward the goal under such a régime.

CHAPTER XXVI

COURSE OF EXOPHTHALMIC GOITER UNDER NONSURGICAL TREATMENT

Duration of Treatment.—Both patient and medical attendant must clearly understand that this is a protracted disease, requiring protracted treatment. The patient must be kept under the influence of the medical attendant for a period of months, perhaps a year or two, depending upon the exigencies of the case. At first calling on the doctor once or twice a week, depending upon the circumstances of the case; as the patient is substantially improved, say at the end of three to six months, *subjective* recovery is reached and visits may be less frequent, the patient calling once every week or two until the first year is over. I regard the first six to twelve months as the period of *active* treatment, during which time almost every act of body and mind is under the doctor's guidance, so that irritating influences, petty obstacles, and other ordinarily unseen factors which tend to deflect from a progression of favorable events are averted. At this time, the average patient has reached a state of *subjective* and *objective* recovery. He is then permitted to resume the ordinary duties of life with or without restrictions as the case may be, and to enjoy a normal social existence. The patient is then made to understand that a secondary period of six months to a year of *passive* treatment has begun. He calls on the doctor once every four to eight weeks during this period, in order that the effects of the prescribed physical and mental activities may be noted, and suggestions, if necessary, may be given. The period of passive observation has for its object the confirmation of achieved results; the minimizing or elimination of the previously existing susceptibility to Graves' disease, in order that relapse may become not only an improbable but an unthinkable event. This period of passive observation is not essential, but highly desirable. The patient's vulnerable physical and mental spots are strengthened; latent or dormant vicious circles are discovered and destroyed; sensitive or thin-skinned natures are modified; the excitable individual is made level-headed,—in brief, the patient's threshold of emotional response is so reinforced as to render him resistant to psychic trauma and the other most common causes of the Graves' syndrome. If the patient is a wage earner and emaciation and heart hurry are not extreme, he is permitted to continue working, with or without reservations. Patients with advanced cases of the disease are permitted to

return to work within six months of treatment, as the substantial improvement renders it safe at this time. Of course the nature of the work must be taken into account.

If I were asked for a general statement regarding the duration of treatment of Graves' disease, I would say the following: The early stage of the disease in which vague symptoms have existed for several months is usually entirely curable within six to twelve months. The frankly outspoken syndrome of one to several years' duration in which there has been very evident partial or total disability because of nervous and physical deterioration requires approximately one year of active treatment and another year of passive observation. The very severe forms of the disease in which there has been a considerable degree of myocardial degeneration are usually cured within the same length of time as the preceding, but there are many exceptions to this rule. The individual may become subjectively normal, but still remain a patient from an objective viewpoint because of the cardiac and other sequelæ. This, of course, would require a more or less continuous vigil for yet another year or two, not of the Graves' syndrome, but of the heart; such a patient, though cured of the Graves' syndrome, might require a cardiologist's attention. It might be stated, however, that with few exceptions all patients are in a condition to be discharged cured of Graves' disease within a period of from six to eighteen months.

Course of Clinical Events.—The course of Graves' disease under appropriate treatment as herein advocated depends upon many circumstances, among which are such factors as influence the prognosis, already discussed. In the average patient, the first result of successful therapy is a substantial slowing of the pulse; this is associated with a disappearance of precordial discomfort, an increase in weight, improved sleep and a disappearance of nervousness, an oncoming sense of well-being, and finally a disappearance of the tremor, thyroid swelling and of exophthalmos. The thyroid and eyes may improve in direct proportion with improvement elsewhere, but if the goiter was unusually large and exophthalmos extreme, these may not become normal for weeks or months following the disappearance of all other active manifestations of Graves' disease. This does not mean that the patient has not recovered; it merely indicates that the process of absorption of a pathologic redundancy of retro-orbital fat, blood vessels, and other factors, real or hypothetical, is a very slow procedure. The facility with which this process occurs depends in large measure upon the previous duration or chronicity of the affection. Occasionally, however, the exophthalmos and other eye signs improve first, with general recovery sometime later. Generally speaking, in a patient cured of a Graves' disease of one year's duration, the exophthalmos may disappear within six months following the institution of treatment. In one having suffered with Graves' disease for ten or more years, the eyes may not

resume their former appearance for a year or two following recovery from the disease. Sooner or later, however, the exophthalmos disappears, and the eyes are restored to normal.

In brief, the course of events tending toward recovery is in most patients the direct opposite to what we observe during the development of the disease. Within a few months the clinical picture closely resembles the incipient form of the disease, and a short time later pre-Graves' stage is reached, in which the heart is normal at rest, but may flare up moderately through physical or emotional strain. But rational treatment does not stop at this point; it does not permit even of predisposition, as this means a susceptibility to relapse. Hence when the heart rate has reached normal, though all the other manifestations of the illness have by this time disappeared, the patient is kept under observation for several months or a year longer. During this time, the influence of the medical attendant over the patient makes for permanent physical and mental reconstruction. The patient is taught how to work, how to play, how to sleep, and even how to think. Thus, the formerly susceptible individual soon becomes as immune to Graves' disease as anyone else; relapse becomes highly improbable, and the patient, taught how to live and imbued with a healthy philosophy of life, now begins to enjoy unprecedented health and is more useful than ever to self and society.

Indices of Improvement and Recovery.—The best index of improvement in a patient under treatment of Graves' disease is a reduction in catabolism and an increase in anabolism as represented by a reduction in basal metabolism. In the absence of calorimetric determinations, improvement is indicated by an increase in weight and a reduction in heart rate. A restoration to normal of the weight and heart rate is synonymous with recovery of the patient, for when these factors obtain, all other symptoms of the disease have either disappeared or are disappearing.

Finally, I would state that since January, 1919, the subjective and objective recovery of nearly all patients under my observation is confirmed by normal basal metabolism figures. Also for years following the periods of active treatment and passive observation, I make it a rule to keep informed regarding the future health and usefulness of the individual. This is usually accomplished by a social visit from the patient semi-annually or annually. I have thus kept in touch with many of my patients for more than 10 years and am happy to state that they are not only free from evidences of Graves' disease, but are in better health than ever before.

ILLUSTRATIONS OF COURSE OF EXOPHTHALMIC GOITER WHILE UNDER NONSURGICAL MANAGEMENT



FIG. 88.—Exophthalmic goiter of 4 years' duration. Pulse rate 100; basal metabolism plus 48; weight 179½ pounds.



FIG. 89.—Same patient as in Fig. 88 after 4 months of treatment while at work. Exophthalmos* though still present is improved; thyroid gland is normal; pulse rate is 70, basal metabolism is plus 14, and there is a gain of 30 pounds in weight.



FIG. 90.—"Forme fruste" type of Graves' disease of 3 years' duration. Heart rate 100; weight 120 pounds.



FIG. 91.—Same patient as in Fig. 90, after 3 months of treatment while at work. Heart rate is 72, and there is a gain of 23 pounds in weight.

* As mentioned elsewhere, exophthalmos in Graves' disease is most likely produced by irritation of the cervical sympathetic. Following proptosis there occurs an accumulation of fat in the space behind the eyeball. When the patient recovers, though the cervical sympathetic is no longer stimulated, exophthalmos may still persist for a variable time because of the persistence of the pad of fat behind the eyeball. This is especially true in patients who have gained greatly in weight. In the course of time, however, there occurs an adjustment of orbital tissues, and exophthalmos finally disappears. In the *average* patient exophthalmos begins to disappear simultaneously with the disappearance of the other evidences of Graves' disease.

ILLUSTRATIONS OF COURSE OF EXOPHTHALMIC GOITER WHILE UNDER NONSURGICAL TREATMENT



FIG. 92.—Exophthalmic goiter of 3 or 4 years' duration during a crisis. The blurring of the photograph is due to the trembling of the patient while posing. Note the apparent dyspnea, the patient gasping for breath with mouth open. Left eye is artificial but appears exophthalmic because of retraction of lids. Right eye is extremely exophthalmic. Extreme weakness; very large heart with auricular fibrillation; pulse rate about 200 per minute with pulse deficit of about 100 more; basal metabolism plus 96; patient appears as though he might become moribund at any moment.



FIG. 93.—Same patient as in Fig. 92, after 7 months' treatment, progressing toward recovery. Patient can sit without trembling and with mouth closed; exophthalmos has disappeared; heart action is regular and rhythmical with a rate of 72 per minute; the thyroid gland is reduced in circumference by 2 inches and is rapidly approaching normal; basal metabolism is plus 15; there is an increase of 36 pounds in weight, and the patient expresses himself as feeling entirely well. He has now returned to work and will probably be discharged from active treatment within 3 or 4 months.

ILLUSTRATIONS OF COURSE OF EXOPHTHALMIC GOITER WHILE UNDER NONSURGICAL TREATMENT



FIG. 94.—Atypical exophthalmic goiter of 4 years' duration with extreme emotionalism, loss in weight, weakness, basal metabolism plus 52, and a pulse rate of 120 per minute.



FIG. 95.—Same patient as in Fig. 94 eight months later. Recovery with pulse rate of 70, normal basal metabolism, and a gain of 31½ pounds in weight.



FIG. 96.—Graves' disease without exophthalmos in girl of 13. Weight 88 pounds; pulse rate 140; basal metabolism plus 68; circumference of neck 13½ inches; extreme nervousness and complete insomnia.



FIG. 97.—Same patient as in Fig. 96 after 6 months of treatment. There is a gain of 32 pounds in weight, with basal metabolism plus 10. Thyroid, pulse rate and nervous system are normal, and she is ready to resume school work.

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ILLUSTRATIONS OF COURSE OF EXOPHTHALMIC GOITER WHILE UNDER NONSURGICAL TREATMENT



FIG. 98.—Exophthalmic goiter without exophthalmos, of 1 year's duration. Patient is bed-ridden and weighs 88 pounds. Pulse rate 140; extreme palpitation and weakness, basal metabolism plus 76.



FIG. 99.—Same patient as in Fig. 98 after 6 months' treatment. There is a gain of 50 pounds in weight; heart rate is nearly normal, basal metabolism is plus 18, and patient bids fair to be ready for discharge from active treatment within 3 or 4 months. (Patient was permitted out of bed within 2 weeks after treatment was instituted.)



FIG. 100.—Mixed colloid adenomatous goiter with hyperthyroidism, of 6 years' duration. Tachycardia, emaciation, and marked weakness.



FIG. 101.—Same patient as in Fig. 100 after 5 months' treatment. Thyroid nearly normal; there is a gain of 20 pounds in weight; patient will probably be discharged from active treatment within 2 or 3 months.

ILLUSTRATIONS OF COURSE OF EXOPHTHALMIC GOITER WHILE UNDER NONSURGICAL TREATMENT



FIG. 102.—Patient described in next picture (Fig. 103) just prior to onset of exophthalmic goiter.



FIG. 103.—Same patient as in Fig. 102. Exophthalmic goiter of 7 years' duration. Weight 101 pounds; pulse rate 140; basal metabolism plus 78; extreme weakness; tremor; exophthalmos and hyperplasia of thyroid. Circumference of neck 15 inches.



FIG. 104.—Same patient as in Fig. 103 after 8 months of treatment. Weight markedly increased; pulse rate, basal metabolism, eyes, and neck approaching normal. Circumference of neck reduced by nearly 2 inches.

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ILLUSTRATIONS OF COURSE OF EXOPHTHALMIC GOITER WHILE UNDER NONSURGICAL TREATMENT



FIG. 105.—Atypical Graves' disease without exophthalmos and goiter, of about one year's duration. Extreme weakness, tremor, nervousness, palpitation, and insomnia. Heart rate 94; weight $118\frac{3}{4}$ pounds; basal metabolism plus 38.



FIG. 106.—Same patient as in Fig. 105, nine months later. Complete restoration to health and usefulness, with a normal pulse rate and a gain of 25 pounds in weight.



FIG. 107.—Extreme exophthalmic goiter of probably 11 years' duration in a woman of 53. Myocardial degeneration with auricular fibrillation and impending decompensation; basal metabolism plus 76, extreme thyroid hyperplasia, exophthalmos, weakness, and trembling.



FIG. 108.—Same patient as in Fig. 107 following 12 months' treatment. Disappearance of exophthalmos and goiter; heart rate normal, action regular and rhythmical; basal metabolism is plus 12; patient is subjectively and objectively recovered and will be discharged from active treatment within 4 months.

CHAPTER XXVII

CASE HISTORIES AND ILLUSTRATIONS OF DISCHARGED PATIENTS

To illustrate the efficacy of the nonsurgical management of exophthalmic goiter I can do no better than include here the histories and photographs of twenty patients taken at random from my files. In a few of these, especially those who have been discharged cured several years ago, I present no photograph of the patient during the illness, because I was not photographing patients at that time. The idea of taking a picture of patients before and after treatment occurred to me more recently. I find it not only a great source of satisfaction but a pleasure as well to both the patient and myself to have this accurate means of noting the complete transformation from the dramatic expression of Graves' disease to one reflecting perfect health and happiness.

CASE 1, age 39, male, business man, referred January 16th, 1911.

Chief Complaints: Extreme weakness, swelling of the legs and abdomen, palpitation and goiter. Duration of illness 1 year.

Family History: The patient's mother died of carcinoma, his father is living and well. Otherwise the family history is negative.

Previous Medical History: The patient claims never to have been sick prior to his present illness.

Social and Personal History: The patient is married; his wife and 6 children are living and well. His dietary habits are good and his home environments are congenial.

Present Illness: One year ago, following a fright as a result of a practical joke played upon him by a friend, the patient began to suffer with anorexia and general weakness. Shortly thereafter, he discovered that his neck was getting swollen, although he was losing weight. In the course of 3 months the eyes began to bulge, palpitation and precordial discomfort became severe, extreme weakness supervened, loss in weight was becoming alarming, and there was a complete change in the patient's appearance. In the course of 9 months, despite the fact that he had been under various kinds of treatment, the symptoms were becoming alarmingly worse. There was swelling of the ankles, which was gradually extending upward. The abdomen, too, was becoming rather large, which the patient soon discovered was due to "water."

Physical Examination: The patient is a white male, 5 feet 7 inches in height, rather water-logged in appearance, in spite of which he weighs but 135 pounds. There is such extreme weakness that it is surprising to see him still able to walk into the office. The skin is moist and edematous over the legs and abdomen; dermographia is easily elicited. The teeth are in bad

condition. The *tonsils* are congested. The *eyes* are extremely exophthalmic, and all the characteristic eye signs of Graves' disease are present. The conjunctiva is congested, and there is epiphora. The *thyroid* is rather large and is throbbing. The goitrous mass is diffuse. The greatest circumference of the neck is $16\frac{1}{2}$ inches. Palpation reveals a thrill and on auscultation a loud systolic and diastolic bruit is heard. The *heart* is markedly dilated. The apex beat is diffused over almost the entire left side of the chest. The anterior border of the heart extends over into the left axillary space. Auscultation reveals a state of *delirium cordis* with a pulse rate of 160. There is a loud systolic murmur audible throughout the entire chest, the point of greatest intensity being the mitral area. The tricuspid valve, too, is deficient. There is also a loud diastolic murmur over the aortic area. The lungs present evidences of passive congestion and seem to be on the verge of edema. The abdomen is considerably enlarged and presents ascites which renders the skin rather tense but not to the point necessitating tapping. The *limbs* are water-logged, especially below the knees. The *reflexes* are hyperactive, and *tremor* is universally distributed throughout the voluntary muscular system.



FIG. 109.—Recent photograph of patient described in case 1, who, in 1911 was suffering with severe exophthalmic goiter characterized by marked exophthalmos, large hyperplastic goiter and cardiac decompensation with almost complete anasarca. He has been enjoying perfect health since his complete recovery in January, 1912.

and there was a diminution in exophthalmos, goiter, and tremor. Indeed, the patient felt that he was getting entirely well. Progress was continuous, and within 6 months the patient's heart had become entirely normal in size, and there was complete disappearance of murmurs. One year after the institution of treatment the patient was discharged from active treatment and placed upon another year of passive observation. His heart, thyroid, eyes and weight were restored entirely to normal, and he was subjectively and objectively a healthy individual. At this point he was permitted to return to business, to which he is still attending at this writing (April, 1924). He is a picture of perfect health.

Summary: A man of 39 suffering with a very severe form of Graves' disease, circulatory decompensation, and anasarca, was restored to complete subjective and objective health within 12 months of active treatment. He has been active in business ever since, and to this date, more than twelve years later, he is actively engaged in conducting a large ice cream manufacturing plant.

Psychic Condition: The patient is rational and intelligent, and realizes that he is extremely ill. He begs to be assisted, stating that no one has been able to help him, despite the fact that he has had "rest cures" in three different hospitals since the inception of his illness.

Diagnosis: Exophthalmic goiter or Graves' disease of malignant course, with cardiac decompensation.

Course Under Treatment: There was complete coöperation of patient and household with instructions in treatment. Within 2 months, the ascites had disappeared, and the patient weighed 152 pounds, a gain of 17 pounds. Sleep was restful, the pulse was 100,

CASE 2, age 37, housewife, referred July 21, 1914.

Chief Complaints: Precordial distress, palpitation, extreme weakness, goiter, bulging eyes, indigestion, loss in weight, insomnia. Duration of illness about 2 years.

Family History: Negative.

Previous Medical History: The patient states that she had most of the diseases of childhood. Several years ago she had an attack of acute articular rheumatism which kept her in bed 2 weeks. Since then she has had frequent milder attacks of pains in the joints, especially prior to and during changes of temperature and humidity. During the past 2 years, she has been suffering with almost constant attacks of indigestion diagnosed by her physician as nervous dyspepsia. The attacks were characterized by pain shortly after eating, gastric distension, sour eructations, and occasional vomiting.

Social and Personal History: Menstruation began at 13, and had always been regular. She was married at 21, had 6 children, and there were no miscarriages. She is in the habit of taking 5 or 6 cups of coffee daily, and also plenty of carbonated beverages. She takes animal food 2 or 3 times daily, and uses the spices and condiments to excess. Though her social environments are congenial, she was obliged during the past several years to assist her husband in building up a general merchandise business, while at the same time performing her household duties.

Present Illness: About 2 years ago, the patient had what she terms a "nervous breakdown," with an exacerbation of indigestion, palpitation, complete insomnia, swelling of the thyroid, bulging of the eyes, profuse perspiration, hysterical spells, marked loss in weight and anorexia. During this time she felt that she was losing her mind and feared that she would be sent to an asylum. Treatment by local physicians being unsuccessful, she was placed in a large hospital in Philadelphia. At first there was some improvement, but later a complete relapse occurred, and a surgeon was consulted, who advised immediate operation. The patient unconditionally refused to consider operation. Several other consultants were called who likewise advised operation, but this she persistently refused. She was taken home, where she remained suffering with the syndrome continuously, with slight variations. During the past 6 months her eyes have been bulging to such extent that she has been obliged to place pieces of lint over them on retiring in order that the ocular conjunctiva would be protected from excessive irritation. The patient claims that she has not had a good night's sleep for over a year, the insomnia being due to exophthalmos, sweating, nocturia, and extreme restlessness. She has lost 20 pounds in weight during her illness.

Physical Examination: The patient is a white female, 5 feet 3 inches in height, weighing 97 pounds. The skin is warm, thin, and very moist, presenting prompt dermographia, which remains for several minutes before fading. The teeth are in good repair. The tonsils are moderately enlarged and chronically diseased. The eyes present extreme exophthalmos, somewhat greater on the right side. The Dalrymple, von Graefe, and all other eye signs are present. The eyes are very tender and somewhat painful when walking in the sunlight; the eyelids are incapable of coaptation to within $\frac{1}{8}$ of an inch. The conjunctiva is moderately congested. The thyroid gland is uniformly enlarged. The swelling is diffuse and throbs in unison with the cardiac cycles. The vessels of the neck throb violently. Palpation over the thyroid reveals a thrill, and auscultation a loud systolic and diastolic bruit. The greatest circumference of the neck is 14 inches. The heart is enlarged to near the anterior axillary line and downward to the sixth inter-

space. There is systolic thrill over the precordial area. Auscultation reveals a systolic murmur transmitted to the left axillary space and around to the scapula. The second apical sound is short and weaker than normal. The heart rate is 120 per minute. Both sounds over the base of the heart are weak and at times indistinct. The first tricuspid sound is replaced by a soft blowing murmur. The *lungs* are negative, except for the presence of harsh breathing over both bases posteriorly. The *abdomen* presents evidences of slight enteroptosis. There is tenderness over the gastric area and slight veins. The lower *limbs* are moderately edematous from the ankles to the knee joints; the superficial veins are prominent. The upper limbs are negative. The *reflexes* are very much exaggerated. The *tremor* is typical and distributed throughout the voluntary muscular system.



FIG. 110.—Recent photograph of patient described in case 2, who, in 1914 was suffering with a large hyperplastic goiter, very extreme exophthalmos which required the protection of small pads over the eyes to keep them from overexposure during attempts at sleep, and a double mitral murmur from cardiac dilation. She has been free from all evidences of the disease since her discharge from treatment in 1915.

Psychic Condition: The patient presents the typical facies of exophthalmic goiter of extreme form. She lacks continuity of thought, rambling along in the description of her condition until fatigued, and after a brief pause, continues on in her narration.

Diagnosis: Graves' disease in advanced form, with nervous and circulatory predominance in the symptomatology, and with evident impending circulatory decompensation.

Course Under Treatment Progress was tedious and difficult because of deficiency in coöperation, and especially because of the extreme irritability of the gastro-intestinal tract. It was therefore necessary to concentrate quite as much upon treatment of the digestive functions as elsewhere. Moreover, her rheumatic pains were a prominent factor in the symptomatology at this time. Despite these drawbacks, however, there was considerable improvement within 10 weeks. Her weight was now 108 pounds, and there was marked subjective relief of symptoms. Eight months after treatment was begun, the patient was urged to discontinue the use of the small pieces of cloth over her eyes

on retiring, as her exophthalmos hesitated to do, but on trying it, discovered that all was well. At the termination of 11 months of treatment, the patient's weight was 120 pounds, an increase of 23 pounds over the original figure, the heart rate was 76, and the heart area was within normal limits, with a disappearance of murmurs. The edema of the legs had disappeared a long time before. At this time her appetite was perfect, sleep was sound and refreshing, her capacity for work was greater than it had been for years, and her neck was normal in appearance. Fifteen months after the beginning of treatment, the patient was discharged cured. She now weighed 124 pounds and was normal subjectively and objectively in every respect. She was then placed

under passive observation to report to me once in two months during the ensuing year. Though at this writing the patient has been discharged from passive observation for eight years, she drops in to see me when in Philadelphia, to show how well and happy she looks and feels.

Summary: A woman of 37 with advanced Graves' disease, very extreme exophthalmos, thyroid hyperplasia, psychic symptoms, and impending cardiac decompensation, was completely cured of all evidences of her disease and restored to perfect health within 15 months of nonsurgical management.

CASE 3, age 24, female, single, mill hand, referred for treatment November 29, 1917.

Chief Complaints: Goiter, choking sensations, loss of weight and strength, nervousness, palpitation, and excessive sweating.

Family History: A younger sister is suffering with goiter and "nervous dyspepsia"; otherwise the family history is negative.

Previous Medical History: The patient has had most of the diseases of childhood; she has been nervous for several years.

Social and Personal History: Menstruation began at 13 and has always been regular except during the last few years. Her dietary habits are good, and home environments are congenial.

Present Illness: About 4 years ago, a few weeks after a fright, the patient became more nervous than ever and at the same time noticed a swelling at the front of her neck. An evident loss in weight and persistent palpitation caused her to seek medical attention. She consulted several physicians who made varying diagnoses, among which were "nervousness" and "indigestion." When a few months later her neck became very much larger and the eyes began to bulge, the diagnosis was clear, but treatment was unsatisfactory. Excitability, sleeplessness, nausea, vomiting, diarrhea, and great weakness occurred, and caused her physician to urge that operation be performed. This idea she refused to entertain. A year after the onset of symptoms, she was sent to the hospital for a 3 months' rest cure, the result of which was inconsiderable improvement in the symptoms. However, the palpitation, exophthalmos and goiter were unimproved, and she continued to seek advice elsewhere. Operation was again advised, but she persistently refused to submit. At this time she decided to discontinue medical attention and stay at home. During the past several months her symptoms have become very much aggravated.

Physical Examination: The patient is a white female adult, 5 feet 6 inches in height, weighing 125 pounds. The skin is soft and moist, presenting occasional erythematous areas distributed over the face, neck, and chest. Superficial veins over the thyroid are prominent. Dermographia is easily elicited and persists for 4 minutes. The teeth are negative. The tonsils are enlarged and present evidences of chronic inflammation. The eyes present extreme exophthalmos; there is congestion of the conjunctiva, and the patient complains of excessive dryness resulting in an aching sensation. The thyroid is unusually enlarged for a hyperplasia, the greatest circumference of the neck being 15½ inches. The swelling is evenly distributed, presenting a thrill on palpation and a bruit on auscultation. The heart is enlarged to the sixth interspace downward and extends outward to the left midclavicular line. The first apical sound is somewhat prolonged, but there is no distinct murmur. The pulse rate is 100 per minute. The heart action is regular and rhythmical. The lungs, abdomen, and limbs are negative. The reflexes are normal. The tremor characteristic of Graves' disease is present.

Psychic Condition: The patient is rational and intelligent and is very anxious to coöperate and get well in order that she may get married, as she has been engaged for a few years.

Diagnosis: Exophthalmic goiter of 4 years' duration in which the outstanding features are the marked exophthalmos and unduly large hyperplastic thyroid.

Course Under Treatment: Three months after treatment was instituted, the heart rate was 80 per minute; there was a gain of 17 pounds in weight, and all subjective evidences of the disease had disappeared. There was still considerable enlargement of the thyroid and exophthalmos. At the termination of 6 months of treatment there was a distinct improvement in the neck and eyes, and the pulse rate was 70 per minute. The patient now weighed



FIG. 111.—Patient described in case 3, with healthy child. She has enjoyed perfect health since her discharge from treatment in 1918. Though the thyroid gland is normal, there is a peculiar redundancy of skin over the site of the former large goiter.

148 pounds, more than she had ever weighed in her life. A visit from her fiancé to my office at this time disclosed the fact that they would be married as soon as I gave the word. Believing that this would eliminate the strain incident to engaged life, and in view of the fact that the patient's condition was satisfactory, I gave my consent, and they were married the following month. At the termination of the ninth month of observation, she was discharged from active treatment, weighing 152 pounds, a gain of 27 pounds, and entirely well from every possible viewpoint. She was then placed under passive observation, to report to me once a month for the ensuing year. Despite the fact that she became pregnant and that her husband was called to the colors during the War, her health continued unimpaired. About 12 months after discharge from active treatment she was delivered of a fine 9 pound baby girl. The patient made an uneventful recovery from delivery and mother and baby are "living happily ever afterwards."

Summary: A female adult of 24 with Graves' disease of 4 years' duration, was discharged cured after 9 months of active treatment, during the seventh month of which she was married. Permanency of recovery was emphasized by the fact that War conditions, pregnancy, and parturition had no untoward influence upon her health.

CASE 4, age 35, married, housewife, referred for treatment April 29, 1920.

Chief Complaints: Extreme weakness, marked palpitation and nervousness, insomnia, sweating, indigestion, paroxysms of diarrhea. Duration of illness 5 years.

Family History: Negative.

Previous Medical History: The patient states she had most diseases of childhood, except diphtheria and scarlet fever. She has had occasional attacks of sore throat. She was operated on for appendicitis at the age of 20. At 26, following a fall, she was operated on for an injured coccyx, at which time an anterior uterine fixation was also performed.

Social and Personal History: Menses began at 16; she married at 21; has one child, aged 12, who was epileptic. There were no miscarriages. The patient has always been more or less nervous and introspective. Her dietary habits are good.

Present Illness: The patient's symptoms date back to the following incident: One night in March, 1915, while she was fast asleep, she was awakened with a start by a mouse which was crawling over her neck. The sudden scare resulted in complete insomnia and when night after night she would doze off for a while from sheer fatigue, she would be awakened by terrifying nightmares in which the mouse would be a prominent figure. Within 6 months the patient was in a state of total helplessness, with severe palpitation, very rapid heart, and nervous chills. She was placed in bed by her family physician for 6 weeks. This resulted in slight improvement, but she was still an invalid. Extreme weakness, palpitation, nervousness, indigestion, nausea, vomiting, and diarrhea were more or less constant symptoms. In February, 1917, though there was neither exophthalmos nor goiter, a thyroidectomy was performed. The patient had a very stormy operative convalescence. Not only was the thyroid operation productive of no good, but the patient became weaker than ever following this procedure. When I saw her in April, 1920, she was hardly able to stand, presenting all the symptoms herein mentioned, with the following added: Complete giving way of the limbs, marked hyperhidrosis, trembling all over the body, and dyspnea so marked that she was unable to utter more than one short sentence at a time.

Physical Examination: The patient is a medium-statured, very frail, nervous, poorly nourished woman, 5 feet 5 inches tall, weighing 94 $\frac{3}{4}$ pounds. The skin presents marked dermographia and is very moist, showing occasional erythematous areas. The teeth and tonsils are negative. The eyes are negative except for a slight von Graefe sign. The thyroid region presents a neat, semilunar scar of the thyroideotomy performed 3 years before. Examination of the gland indicates the presence of approximately one half of the normal thyroid. The heart shows evidences of slight hypertrophy with dilatation. There is no thrill or murmur; the heart sounds are much weaker than normal and the heart rate is 120. The lungs and abdomen are negative. The reflexes are very much exaggerated. Tremor of the outstretched fingers and toes and practically of the entire body is present.

Psychic Condition: The patient is very emotional; she is extremely introspective, but does not present the characteristic impulsive muscular

movements of Graves' disease. She appears willing and eager to coöperate and get well.

Laboratory Data: The basal metabolism is plus 42, the quinin test is positive; sugar tolerance is moderately reduced.

Diagnosis: Atypical Graves' disease without exophthalmos and without goiter, in which thyroidectomy of the normal sized thyroid had been performed. The exciting cause was probably the aforementioned mouse incident.

Course Under Treatment: During the first 4 or 5 months of treatment great difficulty was encountered because of the irritability of the gastro-



FIG. 112.—Patient described in case 4 —enlargement from a tiny snapshot taken shortly after thyroideectomy, at which time her weight was 94½ pounds, pulse rate was 120, and there was extreme weakness, emotionalism, insomnia and tremor.



FIG. 113.—Same patient as in Fig. 112 after 12 months of nonsurgical treatment. Complete recovery from the Graves' syndrome with a gain of nearly 56 pounds in weight.

intestinal tract, rendering it very difficult to affect a material increase in weight. In course of time, however, these obstacles were overcome, and progress was uninterrupted. Coöperation in treatment was entirely complete and satisfactory, and the patient made satisfactory strides toward health. One year after treatment was begun, the patient weighed 150½ pounds, a gain of nearly 56 pounds, and there was a corresponding improvement in every respect. In brief, the patient became entirely transformed into a normal, perfectly healthy, useful individual, enjoying unprecedented health. Basal metabolism was plus 10. She was then discharged from active treatment, and ordered to return to me once in two months for observation during the ensuing year.

Summary: A married woman of 35 with atypical Graves' disease of 5 years' duration and in whom a thyroideectomy was performed without relief, obtained complete subjective and objective recovery, with a gain of nearly 56 pounds in weight within 12 months of nonsurgical management.

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CASE 5, age 40, business man, referred by Dr. S. Weiss, of New York, January 5, 1923.

Chief Complaints: Distressing palpitation and precordial discomfort, extreme weakness, marked hyperidrosis, nervousness, complete insomnia, and a loss of 50 pounds in weight during the past 6 months. Duration of illness 3 years.

Family History: A sister has diabetes. Otherwise the family history is negative.

Previous Medical History: He does not recall any previous illnesses, except that he began to suffer with "stomach trouble" and constipation 4 years ago.

Social and Personal History: The patient has been married 13 years; he has 2 children who are living and well; his wife had no miscarriages. The patient remarks that he had always been of a nervous, excitable temperament. He has had considerable family unpleasantnesses and friction with relatives, though his relation with his wife is most congenial. He has had 6 years of business worries, which factor seems to have contributed to his illness.

Present Illness: About 3 years ago, he began suffering with palpitation after meals. In September, 1922, he had a sudden severe attack of palpitation, with a pulse rate of 180, which symptoms followed seashore bathing. He was ordered to bed for 4 months, during which time there were spells of incessant nausea and vomiting, complete insomnia, and nervousness involving the psychic faculties. There was also polyuria and a reduction of weight to 99 pounds.

Physical Examination: The patient is a white male adult, about 5 feet 6½ inches tall, weighing 116 pounds. He is extremely nervous, undernourished, and trembling all over. His expression is anxious, and while being examined he became lachrymose. The skin is warm and very moist, and dermographia is marked. The teeth are in good repair; the tonsils are chronically congested. The eyes are slightly exophthalmic; the Dalrymple and von Graefe signs are present. The thyroid is moderately enlarged, especially over the lateral lobes. This organ and the blood vessels of the neck are throbbing violently. Thrill and bruit over the thyroid are quite typical. The lungs present a few moist rales over both bases posteriorly, indicating congestion. The heart on inspection presents all the evidences of marked hypertrophic dilatation, the left border extending to the anterior axillary line and downward to the seventh interspace. The impulse is forcible and diffuse. Palpation presents a distinct systolic thrill over the mitral area. Auscultation reveals a loud apical systolic murmur extending around into the axillary space and quite audible at the angle of the left scapula posteriorly. The second apical sound and the aortic sounds are weaker than normal. The second pulmonary sound is accentuated. The heart cycles are regular; the heart rate is 120 per minute. The abdomen is tympanitic. The reflexes are heightened. Tremor of the outstretched fingers is coarser than usual. Convulsive trembling of the muscles of the entire body occurs every minute or two, during which the patient becomes emotional and lachrymose.

Psychic Condition: The patient is entirely rational, responding to questions promptly and to the point, but there is complete helplessness and lack of morale.

Laboratory Data: Basal metabolism is +52; quinin test is positive; sugar tolerance is moderately diminished.

Diagnosis: Graves' disease with marked accentuation of nervous and

circulatory phenomena. There is myocardial degeneration with relative mitral insufficiency. Prognosis in this case, as it seemed on the primary physical examination, can best be stated in a paragraph from my letter to Dr. Weiss who referred the patient to me for consultation: "The prognosis in this case is guarded because of the myocardium. I believe that with whole-hearted coöperation in treatment on the part of the patient and caretaker (including his household), recovery from the Graves' syndrome should occur within approximately one year.

During this time, myocardial regeneration of sufficient degree may be looked for, so as to enable him to enjoy perfect subjective health and relative usefulness. This, to repeat, is only possible through ideal nursing. It is quite likely, however, that the patient will be required to observe a certain amount of caution regarding cardiac strain for many years."

Course Under Treatment: Since the patient was living in another city, it was difficult for him to call for observation more often than once a month. In the interval of time, he was to remain under the care of his family physician. Four weeks after the preliminary examination he returned to see me. There was a gain of 20 pounds in weight, pulse rate was 72, and the murmur was scarcely audible. Examination of the heart proved that its size was very much reduced, the left border extending merely to the mid-clavicular line. The patient expressed himself as feeling wonderfully improved, and was anxious to know whether he could resume some of his business duties. Of course, he was warned against being over-enthusiastic, and cautioned not to engage in any physical or mental strain until permitted. He was given further instructions in treatment, and ordered to return a month hence. When I saw him again, he appeared as healthy an individual as any one could be. There was a further increase in weight of 12 pounds, the pulse was 72, and heart action was normal. Examination of the heart revealed a complete disappearance of murmur and a restoration of the size of the organ to normal. At this time

FIG. 114.—Patient described in case 5, after 4 months of treatment. There is a restoration of the heart boundary to normal with a disappearance of the loud mitral murmur and of thyroid swelling, with complete restoration of subjective and objective health and a gain of 39 pounds in weight. When the patient applied for his first consultation the day was too cloudy to permit of a good primary photograph. On his return from New York for the second consultation a month later, there was a gain of 20 pounds in weight and such marked improvement in his appearance that a primary photograph was of course an impossibility. I therefore waited until he could be discharged from active treatment, when the above photograph was taken.

the eyes were normal, and the thyroid gland was normal in size. There were no evidences of the formerly severe attack of Graves' disease. A month later his weight was 155 pounds, and the patient expressed himself as experiencing unprecedented health. It was very difficult to keep his enthusiasm within bounds, as he expressed himself again and again anxious to return to business. A month later, his condition being excellent, and basal metabolism normal, he was placed under passive observation, to return once every month during the ensuing year.



Summary: A man of 40 with Graves' disease of 3 years' duration complicated by a badly dilated heart and extreme nervous phenomena was restored to complete subjective and objective health including restoration of the heart to the normal boundary and function and a gain of 39 pounds in weight within 4 months, whereupon he was placed under a period of passive observation.

CASE 6, age 35, business man, referred for treatment October 25, 1921.

Chief Complaints: Nervousness, insomnia, palpitation, weakness, and sweating. Duration of illness about 1 year.



FIG. 115.—Patient described in case 6. Exophthalmic goiter with marked accentuation of nervous phenomena; pulse rate 130 per minute; extreme weakness; hyperplastic thyroid, and asymmetrical exophthalmos.



FIG. 116.—Same patient as in Fig. 115 eight months later when he was discharged from active treatment and returned to business life. Aside from a slight stare of left eye during attention (this is clearing up at present writing) there is complete subjective and objective recovery with a pulse rate of 70 per minute, disappearance of goiter, and a gain of 35 pounds in weight.

Family History: Negative.

Previous Medical History: The patient had the usual diseases of childhood. No other illnesses prior to present illness.

Social and Personal History: He was married 13 years ago; there are no children. He had been smoking excessively, but has discontinued the use of tobacco for several months. He is fond of meats and of a moderate quantity of tea and coffee. He had always been of a "nervous disposition."

Present Illness: About 12 months ago, following a period of physical and mental strain incident to business and an automobile accident in which his wife was thrown out of the car, the patient began to lose weight very rapidly, so that in the course of a few months his weight of 190 pounds was

reduced to 128 pounds. He was placed by his physician in a hospital for a month's rest cure, during which period he gained 5 pounds, following which his weight went up to 134 pounds. Four months ago the patient's weakness became extreme, and there was a sensation of sudden giving way of the legs on many occasions. At times he felt as though his legs were paralyzed. Associated with this, he noticed bulging of the eyes, enlargement of the neck, extreme sweating without provocation, restless sleep, and he was conscious of strangeness of disposition and emotionalism. Palpitation has recently become a severe complaint.

Physical Examination: The patient is a white male adult, 5 feet 6 inches in height, weighing 146 pounds. The skin is warm and moist, and dermographia is very marked. The teeth and tonsils are negative. The eyes present moderate exophthalmos, the left more than the right; all the other eye signs are present. The thyroid is rather full on inspection, presenting considerable hyperplasia on palpation. Thrill and bruit are present. The greatest neck circumference is 15 inches. *Heart:* The left border extends to just outside the midclavicular line. The heart sounds are weaker than normal; the rate is 130 per minute. The lungs and abdomen are negative. *Reflexes* are hyperacute. *Tremor* is marked, involving the entire voluntary muscular system.

Psychic Condition: There is evident the mental and physical activity typical of Graves' disease of progressive nature. The patient at times appears to verge on a psychosis. There is a tendency to ramble in speech, though in greatest part, response to questions is direct and to the point. There is that forced smile of geniality superimposed upon the picture of frozen fright characterizing the disease.

Laboratory Data: Basal Metabolism is plus 60, quinin test is positive; sugar tolerance is moderately diminished.

Diagnosis: Progressive Graves' disease, in which there is an accentuation of mental symptoms, having for its probable exciting cause the aforementioned automobile accident.

Course Under Treatment: Coöperation in this case was satisfactory, orders being obeyed faithfully. In the course of 8 months' treatment, the patient weighed 181 pounds and was completely recovered. Aside from a still persisting slight stare of the left eye, the patient presented no further evidences of Graves' disease, and was discharged from active treatment; basal metabolism at this time was plus 9. Mentally and physically normal, he now went into business again, in which he is at present engaged.

Summary: A patient with progressive typical Graves' disease of 1 year's duration was discharged from active treatment physically and mentally recovered with a gain of 35 pounds in weight and complete subjective and objective recovery as a result of 8 months' treatment.

CASE 7, age 29, housewife, referred November 8, 1922.

Chief Complaints: Nervousness, palpitation, loss in weight, weakness, trembling, shortness in breath, and goiter. Duration of illness 8 years.

Family History: The mother, a sister, and two aunts have goiter. An uncle died of "galloping consumption."

Previous Medical History: The patient had the usual diseases of childhood; influenza in 1921; an operation for an ovarian neoplasm about 8 years ago, at which time the goiter was called to the patient's attention by her physician.

Social and Personal History: Menstruation occurred at 15; the patient was married 5 years ago and has one child 3 years old; no miscarriages.

She admits that she has always been of a nervous temperament since childhood. She partakes moderately of animal food, coffee, and the spices. Home environments are fairly congenial.

Present Illness: The patient was unaware of the existence of goiter when it was called to her attention 8 years ago. Since then it had been growing larger to its present size. Several months ago nervousness asserted itself and has been getting worse. Along with this the patient has been suffering with progressively increasing palpitation, shortness in breath, trembling sensations, extreme weakness, sweating, and marked loss in



FIG. 117.—Patient described in case 7. Severe exophthalmic goiter of 8 years' duration with a complicating major psychosis. Extreme thyroid hyperplasia, marked weakness, palpitation, pulse rate 140, with considerable cardiac hypertrophy. Basal metabolism plus 70.



FIG. 118.—Same patient as in Fig. 117, as a result of 12 months' nonsurgical treatment. Disappearance of exophthalmos and goiter. Patient is entirely rational; and pulse rate is 72 per minute; basal metabolism is normal; there is a gain of 26 pounds in weight with discharge from active treatment and a resumption of household duties. Patient expresses herself as enjoying unprecedented health.

weight. During the past few weeks the goiter has given rise to hoarseness and some dysphagia.

Physical Examination: The patient is a white female, 5 feet 5 inches in height, weighing $93\frac{3}{4}$ pounds. The skin is quite moist and presents marked dermographia. The teeth are in fair condition, and tonsils moderately inflamed. The eyes are markedly exophthalmic and present all the other eye signs characterizing Graves' disease. The thyroid is rather large and presents an occasional nodule, lacking the usual symmetry of hyperplasia. Throbbing is marked; and thrill and bruit over the organ indicate extreme vascularity. The heart is enlarged to the left anterior axillary line, is rather turbulent, its rate being 140 per minute. The lungs and abdomen

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are negative. *Reflexes* are hyperacute, and *tremor* is not only typical but universally distributed.

Psychic Condition: The patient's quickened cerebration has reached the point of considerable lack of continuity of thought. She seems to be in a mental haze, and though she promises obedience to instructions in treatment, it appears doubtful whether she is capable of satisfactory comprehension of the situation.

Laboratory Data: Basal metabolism is plus 70; quinin test positive.

Diagnosis: Advance Graves' disease with an impending major psychosis.

Course Under Treatment: As we anticipated, despite warnings to patient and household that only through faithful coöperation could a restoration to health be accomplished, team work was not forthcoming. Within several weeks the crisis came, and the patient's mind dominated the clinical picture. Orders in treatment were completely disobeyed, and the household became a veritable chaos because of the patient's unmanageableness. It required approximately 5 months of most intensive nursing and psychotherapeutic efforts to bring her about to a rational status, following which progress became satisfactory. At the end of 12 months of treatment the patient was transformed into a perfectly healthy individual in every respect, and was placed on a period of passive observation. Basal metabolism was now normal; the pulse rate was 72; there was complete disappearance of goiter and exophthalmos, and a gain of 26 pounds in weight. At this point the patient was permitted to resume her household duties as an individual discharged from active treatment.

Summary: A woman of 29 with a severe, protracted form of Graves' disease and a complicating psychosis, was restored to complete health and discharged from active treatment after 12 months of nonsurgical management.

CASE 8, age 24, stenographer, referred by Dr. A. Bernstein, of Philadelphia, June 10, 1922.

Chief Complaints: Nervousness, restless sleep, and palpitation. Duration of illness 3 years.

Family History: Negative.

Previous Medical History: The patient had scarlet fever; she does not remember having had any other illness. She has had psoriasis since childhood; this condition is universally distributed and has been a great source of worriment to her.

Social and Personal History: Menstruation began at 13 and had always been regular. Dietary habits are fair. Patient has always been of a more or less excitable and irritable temperament.

Present Illness dates back to approximately 3 years ago, when her usual excitability and irritability became very much worse, this condition being precipitated by an aggravation of the psoriasis. She became very introspective, palpitation and dyspnea occurred on slightest provocation, and weakness became so marked that she was obliged to give up her position.

Physical Examination: The patient is a white adult female, about 5 feet 5 inches tall, weighing 107 pounds. The skin is very moist, the face presents an acneform eruption of moderate degree; there is typical psoriasis covering the limbs and trunk. Dermographia very marked. The teeth and tonsils are negative. The eyes are somewhat brilliant but not exophthalmic, and aside from an imperfect von Graefe sign, they are negative. The thyroid is normal on inspection but unduly palpable. Auscultation over the organ reveals the typical bruit of a hyperplastic thyroid. The lungs are

negative. The *heart* is negative on physical examination except that it is very excitable, the rate being 120 per minute. The *abdomen* is negative. *Reflexes* are normal. *Tremor* of outstretched fingers and toes is typical of Graves' disease.

Psychic Condition is negative except that the patient is very much depressed over her inability to work, her palpitation, and the psoriasis.

Laboratory Data: Basal metabolism is plus 45; quinin test is positive; there is slight diminution in sugar tolerance.



FIG. 119.—Patient described in case 8. Atypical exophthalmic goiter with marked weakness, nervousness, loss in weight, pulse rate of 120 per minute, and a complicating psoriasis.



FIG. 120.—Same patient as in Fig. 119 six months later. Recovery with restoration of eyes and thyroid to normal; pulse rate 72 per minute, and a gain of 24 pounds in weight.

Diagnosis: Graves' disease without exophthalmos and without goiter, probably having for its exciting cause the worriment over the aggravation of the psoriasis.

Course Under Treatment: The régime upon which the patient was placed effected a very satisfactory response within 3 months, at which time there was a gain of 23½ pounds in weight. The pulse was restored to 72 and there was complete subjective and objective recovery. At this point the patient insisted upon returning to work, although at the beginning of treatment I had informed her that it would be necessary to remain at home for a year. Accordingly, and against my advice, she resumed her duties as a stenographer in a busy office and has been at work since. During treatment for the Graves' syndrome an effort was made to influence the psoriasis favorably by including arsenic, calcium sulphid and ichthyol in combination with the drugs which she had been getting. At the end of six months of treatment, the patient expressed herself as "feeling fine" with the psoriasis at least 50 percent improved, and the skin above the shoulders, including the face, entirely normal. At the termination of 10 months' treatment, the

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latter 7 months of which she had been performing her usual duties as stenographer, she was discharged from active treatment, and placed under passive observation as a recovered patient. At this point, the psoriasis was hardly noticeable.

Summary: A young woman of 24 suffering with atypical Graves' disease of 3 years' duration complicated with general psoriasis was restored to complete subjective and objective health within 10 months, with a gain of nearly 24 pounds in weight, and as a coincident, the practical disappearance of the oldstanding psoriasis.

CASE 9, age 31, dentist, referred by Dr. Geo. A. Ulrich of Philadelphia, June 23, 1920.

Chief Complaints: Extreme weakness, especially in the limbs, trembling and sweating. Duration of illness about 3 years.

Family History: Negative.

Previous Medical History: The patient had no diseases of childhood. He was nearly drowned at the age of 8. He had Spanish influenza during the epidemic of 1918. He struck his head against a wooden beam 5 years ago and was stunned for a few moments. The patient believes this to be a contributing cause of his present condition.

Social and Personal History: He was married 5 years ago and has 2 children. His wife had one induced miscarriage. The patient was a druggist up to 1911, following which he studied dentistry and began practicing in 1915. He has always been of a nervous temperament, extremely ambitious, eager to take up anything requiring mental application, but examinations were always a terrific strain. He is very fond of coffee and meats.

Present Illness: In the spring of 1917 (3 years before), the patient noticed that he was trembling when using dental instruments. At the same time, weakness in the legs was a troublesome complaint. This latter symptom in course of time became so severe as to lead to a sudden giving way of the legs—a feeling of sudden paralysis, without warning and in any locality in which he might find himself and frequently on the street. This led to considerable embarrassment, because when away from home he felt that an occurrence of this sort would give rise to the suspicion on the part of passersby or friends that he might be under the influence of liquor. The spells would last a few minutes when gradually his strength would return in sufficient degree to enable him to continue on his way. Soon there developed swelling of the thyroid, staring of the eyes, emotionalism, sleeplessness, and a greater degree of trembling than ever. Eight months ago, the patient developed an alveolar abscess which was operated upon, resulting in extreme toxemia lasting 12 days. This was followed by an aggravation of all his former symptoms to such an extent that he was unable to continue his practice. There was a loss of 25 pounds in weight.

Psychic Condition: The patient presents the typical mind of typical Graves' disease. Though in the abstract he is rational and intelligent, the patient evinces a flow of ideas irrelevant one to the other; there is a tendency to self-aggrandizement in the matter of mental achievements and ambition. There is considerable introspection regarding subjective symptoms, and no deficiency of assurances that he, as a professional man, fully understands the value of coöperation.

Physical Examination: The patient is a white male, 5 feet 6½ inches tall, weighing 125½ pounds. The skin is warm and unduly moist; dermographia is very marked. The teeth are under repair. The tonsils are in fair condition. The eyes present slight exophthalmos; all the other eye signs are

present. The *thyroid* is moderately enlarged, presenting a hyperplastic goiter, with a maximum circumference of the neck of 15 inches; thrill and bruit are very marked. The *heart* is hypertrophied, the left border extending to just within the anterior axillary line. The first apical sound is prolonged, the second somewhat weaker than normal. There are no murmurs. The heart rate is 120 per minute. The *lungs* and *abdomen* are negative. *Reflexes* are exaggerated.

Tremor is remarkably accentuated, and though the frequency of excursions is the usual seen in exophthalmic goiter, their altitude is far greater



FIG. 121.—Patient described in case 9. Exophthalmic goiter with accentuation of nervous phenomena. Pulse rate 120; weight $125\frac{1}{2}$ pounds; slight exophthalmos.



FIG. 122.—Same patient as in Fig. 121 a year later. Recovery with restoration of heart rate to 70; there is a gain of 30 pounds in weight, and a disappearance of exophthalmos. He is now actively engaged in his profession.

than that of most patients. Also, there is very evident tremor of the entire body, so that placing one's hand upon his shoulder would indicate perpetual vibration of the voluntary muscles.

Laboratory Data indicate Graves' disease of severe type.

Diagnosis: Graves' disease progressing on toward a crisis.

Course Under Treatment: Despite faithful promises to co-operate religiously, there were occasions during which I was obliged to warn the patient that unless promises were reasonably fulfilled, I would refuse further treatment. Indeed, it was necessary for me to enlist the moral assistance of certain sensible relatives and friends in the interests of obedience to instructions. He was possessed of a peculiar spirit of *wanderlust* which led him suddenly to make trips to the shore and elsewhere without notifying anyone, thus absenting himself from treatment for weeks and months at a time, during which active treatment should have been most diligently applied. At last, after pressure was brought to bear on him from all sides, including a final warning from myself (and this happened at the time of a relapse fol-

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lowing extreme infractions of the elementary dictates of common sense), he made a final promise that this time coöperation would be satisfactory. He was now indeed sincere, as was proved by the results obtained during the ensuing few months of treatment. A year after treatment was begun, 6 months of which were spent in disobedience to orders, the patient expressed himself as "feeling fine" and anxious to return to his profession. This he was permitted to do, for there was a gain of 30 pounds in weight, pulse rate was 70, eyes and thyroid were normal, and there was complete subjective and objective recovery. There was a transformation, not only physically, but mentally. The patient's demeanor was now cool and collected. He was able to discourse continuously upon a topic without changing the subject. He was now in a state of mind in which he realized the full responsibilities of the future and was determined to stay well. His very poise was one of slow, collected deliberation, and there was a total absence of those choreiform activities of mind and body which formerly characterized his person. In brief, there was a complete restoration of the patient to physical and mental health. He was now discharged from active treatment and placed upon passive observation, to report once in two or three months.

Summary: A man of 31 with progressive Graves' disease of about 3 years' duration and almost complete lack of coöperation during the first few months of treatment, was restored to subjective and objective health and usefulness within 12 months.

CASE 10, age 11, schoolgirl, referred by Dr. Edith M. C. Weber, of Philadelphia, August 13, 1920.

Chief Complaints: Nervousness, restless sleep, poor appetite, weakness. Duration of illness uncertain.

Family History: Negative.

Previous Medical History: The patient had whooping cough and chicken pox.

Social and Personal History: She had not yet menstruated. She is attending school, but is frequently obliged to stay home on account of nervousness. Dietary habits are fair.

Present Illness: The illness began insidiously, the mother stating that patient has always been more or less frail and nervous, which condition has become accentuated during the past year or two. The neck has recently become swollen, and there is a sensation of trembling, which she first noticed several months ago. There is increasing restlessness during sleep, and the patient appears continuously fatigued and weary. A few months ago the mother thought she observed an undue prominence of the eyes, which condition has recently become aggravated.

Physical Examination: The patient is a white female child, weighing 63 pounds, rather nervous and appearing frail and anemic. The skin is cool and moist, and dermographia is easily elicited. The teeth and tonsils are in fair condition. The eyes present slight exophthalmos, with the Dalrymple and von Graefe signs present. The thyroid is moderately enlarged, especially at the isthmus, and there is a soft systolic murmur on auscultation. The heart is negative; its rate is 120 per minute. Lungs, abdomen, and reflexes are negative. Tremor of outstretched fingers is typical.

Psychic Condition: The patient is rational and intelligent; she is rather self-conscious, especially on account of stuttering.

Laboratory Data indicate Graves' disease of moderate severity and progressive nature without tangible exciting cause.

Course Under Treatment: As there was complete coöperation in obedi-

ence to instructions, the patient was permitted to continue attending school after the third month of treatment. Within 12 months the patient was restored to perfect health; there was an increase of 12 pounds in weight; the thyroid, eyes, and nervous system were entirely normal, and as laboratory



FIG. 123.—Patient described in case 10. Graves' disease in a girl of 11. Extreme nervousness; beginning exophthalmos; hyperplastic thyroid; pulse rate 120 per minute.



FIG. 124.—Same patient as in Fig. 123 when discharged from active treatment. Thyroid, eyes, and heart rate normal. She is completely recovered and has returned to school.

data indicated recovery, she was discharged from active treatment and placed under passive observation.

Summary: A girl of 11 with moderate Graves' disease of insidious onset was restored to perfect health after 12 months of treatment.

CASE 11, age 38, spinster, saleslady, referred for treatment by Dr. Edith M. C. Weber, of Philadelphia, April 16, 1921.

Chief Complaints: Nervousness and insomnia. Duration of illness is said to be 6 months, but appears to be several times the stated period.

Family History: There is a vague history of insanity in the family. The father is suffering with "nervous indigestion."

Previous Medical History: The patient had whooping cough, measles, and chicken pox as a child, typhoid fever at 18, followed by a "nervous breakdown."

Social and Personal History: Menstruation began at 13; duration of each period is prolonged, but its occurrence is regular. She had always suffered with headaches during school life. Her home environments are fair. She has frequent disagreements with her father. Her dietary habits are good. Her mother ventures to remark that the patient has always been of an extremely sensitive and emotional nature, and that she has always been rather nervous.

Present Illness: This is a continuation and an accentuation of previous nervousness, sensitiveness and emotionalism. About 6 months ago, while her mother was away from home, she had an unusually severe quarrel with her father, which resulted in hysteria, complete insomnia and marked irritability. From that time on, weakness, loss in weight, excessive perspiration, and enlargement of the neck became prominent symptoms.

Physical Examination: The patient is a white female, 5 feet $5\frac{1}{2}$ inches in height, weighing 129 pounds, appearing rather dazed while under examination. The *skin* is normal in moisture and texture, excepting an occasional acneform eruption over the face. Dermographia is moderate. The *teeth* are negative. The *tonsils* are not enlarged but moderately congested. The *eyes* present slight exophthalmos. Dalrymple's and von Graefe's eye signs



FIG. 125.—Patient described in case 11. Exophthalmic goiter without exophthalmos. Pulse rate 120 per minute; there is a complicating psychosis.



FIG. 126.—Same patient as in Fig. 125, eighteen months later. Complete physical and mental recovery with pulse rate of 72 per minute, disappearance of goiter, and a gain of 23 pounds in weight.

are present; other eye signs are questionable. The *thyroid* presents moderate enlargement over the isthmus and right lobe, which, on physical examination presents an admixture of adenomatous and hyperplastic characteristics. The *heart* is enlarged to outside of midclavicular line. Heart rate is 120 per minute. There is no murmur, but the heart sounds have greater muscular element than normal. The *lungs* and *abdomen* are negative. *Reflexes* are acute. *Tremor* is typical and universally distributed.

Psychic Condition: The patient appears unable to orient herself. She is somewhat deaf and when questions are almost shouted into her ear she appears lost for a second or two, then responds to the point, but assumes a blank expression and looks into space immediately afterward. The facies are those of a person in whom there is an impending mental crisis. Before leaving my office she asks repeatedly how long it will be before she will be permitted to return to her position, and insists that she is "all right."

Laboratory Data indicate moderate Graves' disease. Basal metabolism +46; quinin test positive.

Diagnosis: Graves' disease of moderate severity and uncertain duration.

Course Under Treatment: While at first fairly coöperative, the patient soon became disobedient and unmanageable. Despite the efforts on the part of her parents and relatives, and my own efforts, during which I made various forms of appeal, it became evident that the patient was verging on a major psychosis. During the fifth and sixth months of her treatment, the symptomatology was complicated by delusions, hallucinations, illusions, complete insomnia, and a total distrust of all persons whose efforts were directed in her behalf. Food, medicine, and even water were regarded as poisons, and she was in constant fear of being poisoned by someone about her. She made several attempts to throw herself out the bedroom window, so that it was necessary to keep a constant vigil. During moments of semi-lucidity she would talk upon religious matters only, and would suddenly throw herself upon her knees, assuming an attitude of prayer. Believing that an appeal through her religious feelings might finally serve as an entering wedge into her inner self and dispel the mental aberration, I had several conferences with her minister, and finally, following a struggle during which we thought we would lose out, there came the dawn of rationality, and in course of time, the results of treatment were very evident. One year after the beginning of treatment, the patient was so well that I permitted her to return to work, believing that this would assist in confirming her recovery. Work was almost an obsession with her from the very start. Six months later, or after 18 months of active treatment, she was discharged, cured in every respect, subjectively, objectively and mentally as well as physically. She now weighed 152 pounds, a gain of 23 pounds; the pulse rate, neck and eyes were normal. In brief, she was, according to her mother, an entirely changed person, and never appeared and acted as well in her life. Basal metabolism at this time was plus 11.

Summary: A patient with Graves' disease of uncertain duration, and with marked mental symptoms, was discharged completely cured and returned to work following 18 months of active treatment.

CASE 12, age 28, housewife, referred for treatment March 17, 1921.

Chief Complaints: Weakness, troubled sleep and discomfort over the heart. Duration of illness 8 years.

Family History: Three brothers died of tuberculosis. Mother died suddenly of heart disease; father died of arteriosclerosis at 68.

Previous Medical History: At the age of 4 the patient swallowed a large grape which caused bleeding from the stomach and convulsions. At 10 she had scarlet fever which required 1 year for recuperation. She had "typhoid symptoms" at the age of 11, which kept her in bed for 3 weeks. Following this, she had measles, and at 12 she had pneumonia.

Social and Personal History: Menstruation began at 17. She had a love affair at 17 which upset her nervous system very much. She married at 20; had an abortion performed 2 months later; a spontaneous miscarriage occurred 6 months thereafter. She describes her usual temperament as "nervous since birth, irritable, hasty, moody and whimsical." She eats flesh food once daily and takes 2 cups of coffee and 4 cups of tea each day. Her home environment is one of continuous strife and warfare with her husband.

Present Illness: The patient believes her present plight to be due to trouble with her husband from the very first month of her life with him.

He goes on a rampage of drunkenness several times a week, during which he becomes maniacal and dangerous. A few months after their marriage, during a drunken orgy, he seized a knife and attempted to commit suicide and attack her at the same time. Shortly thereafter the patient became very nervous and began to notice enlargement of the neck. Subsequent symptoms were occasional fainting spells and palpitation, throbbing sensations in the head and neck, and trembling. About 4 years ago, her eyes began to bulge, and this was followed by an incessant aching in the eyeballs. A doctor whom she consulted prescribed thyroid tablets, which caused an extreme exacerbation of all symptoms, especially those referable to the



FIG. 127.—Patient described in case 12. Exophthalmic goiter of 8 years' duration, with acromegalic features. Neck circumference 15½ inches; heart rate 90 per minute; exophthalmos, extreme weakness and nervousness.



FIG. 128.—Same patient as in Fig. 127, one year later. Complete recovery with increase in weight, disappearance of exophthalmos, reduction of neck circumference by 1½ inches with disappearance of goiter, and heart rate of 70 per minute.

eyes. During the past 2 or 3 years, dyspnea has become very troublesome; there is an occasional paroxysm of dry cough, and her nervousness and restlessness during the night have become very much aggravated. Though the patient now weighs 148½ pounds, she asserts that a short time after she was given thyroid tablets her weight was reduced to 107 pounds. Her weight prior to the onset of illness was 140 pounds.

Physical Examination: The patient is a white female, 5 feet 7 inches in height, weighing 148½ pounds. Her features present a combination of Graves' disease and acromegaly. The skin is unduly moist; dermographia is present. The teeth and tonsils are negative. The eyes present moderate exophthalmos, and all the other characteristic eye signs are present. The thyroid is moderately hyperplastic, presenting a symmetrical, diffuse goiter. Thrill and bruit are present. The greatest circumference of the neck is

15 $\frac{3}{4}$ inches. The heart is moderately hypertrophic and the sounds are somewhat more violent than normal. The heart rate is 90 per minute; there are no murmurs. The lungs and abdomen are negative. The reflexes are normal. The tremor is typical of Graves' disease.

Psychic Condition: The patient is rational, cool, and collected, answering questions promptly and to the point. There is a strong tendency to narrate with extreme detail the varying differences that have arisen during her life with her husband. She also goes into great detail regarding her various periods of treatment under numerous doctors, and her experiences under thyroid otopharmacy.

Laboratory Data: Basal metabolism plus 38; quinin test positive, carbohydrate tolerance normal.

Diagnosis: Graves' disease of 8 years' duration, complicated by evident pituitary involvement. The exciting cause here was her husband's attempt to take her life.

Course Under Treatment: The progress of the patient under treatment was very satisfactory. The clinical picture of the patient did not require any strict regimen of rest. She was therefore permitted to continue her usual duties, appearing in my office once a week for the first 3 months, and once every 2 weeks thereafter until the termination of a year of treatment. At this time, the patient's heart rate, eyes, thyroid, skin, and other evidences of Graves' disease had cleared up. Her neck measurement was now 14 $\frac{1}{4}$ inches, with a normal thyroid, and as her weight had been satisfactory at the outset, I deemed it unnecessary to have her exceed 152 pounds. Of course, the slight leonine feature of pituitary involvement could not be cleared up. The patient having made a complete recovery from the Graves' syndrome, was discharged from active treatment. Basal metabolism was now plus 4.

Summary: A woman of 28 with Graves' disease of 8 years' duration made complete recovery and was discharged cured at the termination of 12 months of treatment.

CASE 13, age 21, housewife, referred for treatment by Dr. S. A. Lowenburg, of Philadelphia, September 17, 1920.

Chief Complaints: Nervousness, palpitation, dyspnea, insomnia, weakness, swelling of the neck, and bulging of the eyes. Duration of illness one year.

Family History: Mother is nervous, otherwise family history is negative.

Previous Medical History: The patient has had measles. She has had frequent attacks of tonsillitis and 5 years ago had an attack of influenza.

Social and Personal History: Menstruation began at 13 and had always been regular and normal. She married 14 months ago. Her married life has been unhappy because of temperamental incompatibility. Her dietary habits are fair. The patient stated that she has always been of a nervous temperament.

Present Illness: Her symptoms began shortly after marriage. Frequent quarrels with her husband brought on an exaggeration of her habitual nervousness, restless sleep, and palpitation. Two months after she was married a miscarriage occurred, and a month later she was operated upon for the removal of an ovarian cyst. Following these incidents the patient's symptoms became aggravated, and nervousness, enlargement of the neck, shortness in breath, weakness, and loss in weight were added to already existing symptoms. About 2 months ago she noticed that her eyes were bulging.

Physical Examination: The patient is a white female, 5 feet 4 inches tall, weighing 107 pounds. The *skin* is moist; dermographia is easily elicited. The *teeth* are negative, the *tonsils* badly diseased. The *eyes* present moderate exophthalmos and the other typical signs of Graves' disease. The *thyroid* is moderately enlarged; it is diffuse and symmetrical, presenting thrill and bruit. The *lungs* are negative. The *heart* boundaries are normal; its sounds are stronger than normal and the rate is 110 per minute. The *abdomen* presents a scar of previous operation, the *reflexes* are acute, and *tremor* is very marked.

Psychic Condition: The patient is very talkative, extremely vacillating in the flow of ideas, very introspective, repeatedly asking whether she is about to die of heart disease and whether the heart would suddenly stop,



FIG. 129.—Patient described in case 13. Exophthalmic goiter with moderate thyroid swelling and exophthalmos; pulse rate 110 per minute; weight 107 pounds; weakness and extreme nervousness.



FIG. 130.—Same patient as in Fig. 129, after 12 months of treatment. Complete recovery with disappearance of exophthalmos and of goiter; pulse rate is 70 per minute, and there is a gain of 34 pounds in weight.

and at the same time giggling with an air of bravado. Ideas and muscular movements are impulsive and aimless at the expense of attention.

Laboratory Data indicated progressive Graves' disease of average severity.

Diagnosis: Graves' disease of one year's duration having for its exciting cause the sudden onset of psycho-sexual tumultuousness of discordant married life.

Course Under Treatment: Because of the patient's mental condition, coöperation was neither satisfactory nor whole-hearted. In the course of a month or two of treatment, I found it necessary to have a confidential talk with her husband on the subject of teamwork in treatment, the outcome of which seemed very discouraging, as he was quite as unreasonable in his attitude as she was in her psychic helplessness. Through a fortunate coincidence, however, the patient left her husband to live with her mother,

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and improvement became more satisfactory. After 4 months of treatment the patient was very much improved, the pulse rate was reduced to 70, the thyroid was normal, and the weight had increased by 23 pounds, but she still complained of occasional palpitation and occasional dyspnea, and there was still that instability of mentality. At this time tonsillectomy was performed. This resulted in a marked exacerbation of all the symptoms, especially the heart rate. Three months later, however, she was again restored to complete somatic health. The mind, too, had become more stable than ever, and because of the sense of well being, she was desirous of taking a position as stenographer. This I permitted her to do as a test. It was unnecessary for her to continue working for more than a few weeks, however, for she became reconciled with her husband. I deemed it feasible to have another confidential chat with the young man, and this time he admitted his former hastiness and unreasonableness, and promised to do all in his power to maintain a state of concord with his better half forever afterward. The patient was discharged after 12 months of active treatment, weighing 141 pounds, with a pulse rate of 70 and complete restoration to normal of the thyroid gland and eyes. She was now enjoying perfect subjective and objective health. She was then placed under passive treatment to call on me once in 3 months during the ensuing year.

Summary: A young woman of 21 with Graves' disease of a year's duration and with an accentuation of mental symptoms made a complete recovery, with a gain of 34 pounds in weight and complete restoration of physical and mental self, after 12 months of active treatment.

CASE 14, age 16, schoolgirl, referred by Dr. L. H. Jacob of Philadelphia, February 1, 1922.

Chief Complaints: Goiter, palpitation, sweating, nervousness, limbs "cave in" and are weak. Duration of illness 18 months.

Family History: Negative.

Previous Medical History: The patient had chicken pox, measles, rheumatism at 7, and frequent tonsillitis.

Social and Personal History: Menstruation began at 12, but had always been irregular and scanty. She is fond of meat, tea, the condiments and candy. The patient is an only child and finds her home atmosphere quite congenial. She has been rather nervous during the past few years.

Present Illness began shortly after the death of her grandmother, which occurred about 18 months before. This served as a psychic trauma, following which the patient's neck became swollen, nervousness developed, the eyes began to stare, and there was weakness, insomnia, excessive perspiration, and emotional outbreaks. She describes herself as being easily scared. During the past several months shortness of breath, palpitation and diarrhea had been rather troublesome.

Physical Examination: A well nourished, white female, weighing 145 $\frac{1}{4}$ pounds, height 5 feet 5 inches, with the usual expression of exophthalmic goiter, except that the eyes are but slightly exophthalmic. The skin presents marked dermographia and is typically moist and erythematous. The teeth are in good repair. The tonsils are congested and cryptic. The eyes are slightly exophthalmic. All the eye signs of exophthalmic goiter are present. The thyroid is moderately swollen, neck circumference is 14 $\frac{3}{8}$ inches, the goiter being smooth and symmetrical, the right lobe slightly larger than the left. The thyroid mass is yielding to the touch and compressible, and presents a slight thrill and a very distinct bruit. The heart is slightly larger than normal and the apex impulse is rather violent. No murmurs are

heard; the heart rate is 150. The *lungs* and *abdomen* are negative. *Reflexes* are hyperactive. *Tremor* of the outstretched fingers and toes is typical.

Psychic Condition is characteristic of Graves' disease. There is emotionalism. She is easily aroused to mirth or tears; speech is quick, movements impulsive. She is inclined to regard orders in treatment as too severe, for they interfere with dancing and swimming.

Laboratory Data: The basal metabolism is + 62; quinin test is positive. Blood and urinary examinations indicate slight carbohydrate intolerance.

Diagnosis: Graves' disease probably preceded by puberty hyperplasia, the shock of her grandmother's death being the probable exciting cause.



FIG. 131.—Patient described in case 14. Exophthalmic goiter with moderate exophthalmos and goiter, extreme weakness and emotionalism. Pulse rate 150 per minute; neck circumference 14% inches.



FIG. 132.—Same patient as in Fig. 131, after 8 months of treatment. Recovery with pulse rate of 70 per minute, disappearance of exophthalmos, reduction of neck circumference by 1½ inches with disappearance of goiter, and a gain of 24% pounds in weight.

Course Under Treatment: Because of her immaturity of mind, it was frequently necessary to warn the patient that strict obedience to instructions in treatment is the only means to health and to life itself, and that unless obedience was forthcoming, treatment would be refused. The mother was also urged to permit no compromise in strict obedience. The patient was placed on a regimen of hygiene, rest, diet, drugs, electricity, and psychotherapy. There was considerable difficulty in keeping her within bounds in matters of rest, sleep and diet, her attitude necessitating repeated warning and urgings to do better. In July, 1922 (5 months later), the patient was practically cured. At this time, while walking about in the public park, she collided with another girl on roller skates. She was moderately bruised and cut, but no exacerbation occurred. (The patient stated that she was so calm about the incident, laughing and joking while her bumps were being

fixed up, that the other girl remarked: "You would dance in your coffin!" Her weight was now 170 pounds, neck circumference 13½ inches (normal), heart rate was 70, eyes normal, mental attitude the average for a girl of her age and social stratum, the patient being subjectively and objectively cured. This being confirmed by laboratory data, she was placed on an 8 months' period of passive observation, reporting to me every month.

Summary: A girl of 16 with atypical Graves' disease of 18 months' duration obtained a complete subjective and objective recovery after 5 months of nonsurgical management, and was discharged 8 months thereafter.

CASE 15, age 22, college student, referred by Dr. S. B. Pole, of Washington, D. C., November 20, 1921.

Chief Complaints: Weakness, palpitation, goiter, recurrent diarrhea, restless sleep.

Family History: Parents are living and well. Two maternal aunts have goiter. Duration of illness about 6 months.

Previous Medical History: At the age of 5 there was acute adenitis, which was allayed by medical treatment. At 7, tonsillotomy was performed. Between the age of 7 and 14, patient had measles, whooping cough, and mumps. At 14, coincidental with the onset of menstruation, there was a slight swelling of the thyroid which persisted in after life. Up to the age of 20, the patient presented very tender parotid glands. In January, 1920, the patient had an attack of tonsillitis with quinsy, and another in April. In July, 1920, tonsillectomy was performed. This resulted in a clearing up of the parotid tenderness, but with an onset of nervousness and excitability. In April, 1921, while teaching in the public schools, the patient had an attack of purulent conjunctivitis, and the following month, an attack of influenza. This latter, according to her father, who is a physician, was the beginning of the onset of the patient's syndrome.

Social and Personal History: Menstruation began at 14, and had been rather irregular, especially during the past year. The patient had been actively engaged in college work up to the time of the onset of her illness. In temperament, she is outwardly not at all irritable or excitable, and states that she is rather reserved in her disposition. Study is an obsession with her. Her home life is most congenial. Her relations with friends and relatives are most cordial. Her dietary habits are good.

Present Illness began about 6 months before, following an attack of influenza. The thyroid became rapidly swollen. Extreme nervousness, hyperdrosis, trembling, insomnia, and tachycardia asserted themselves in rapid sequence. After a brief rest in bed which resulted in improvement, she insisted on going away to college in a distant city, but was sent back 5 weeks later by the physician in charge of the infirmary, because of an attack of "thyroid symptoms." At this time, gastro-intestinal symptoms had developed, with intermittent attacks of diarrhea.

Physical Examination: (The examination was made at the patient's home in Washington, as she was too ill to leave her bed). The patient is a white young woman, about 5 feet in height, weighing 89 pounds. The skin is warm and unduly moist, and dermographia is marked. The teeth are in good condition. The tonsils have been removed. The eyes present slight exophthalmos; the Dalrymple and von Graefe signs are present. The thyroid is moderately enlarged, the circumference of the neck being 13½ inches. The swelling is diffuse and throbbing; there is no thrill on palpation, and on auscultation a bruit is audible, but rather distant. The gland pathology is possibly that of a mixed hyperplasia and adenoma. The heart is slightly



Figs. 133 and 134.—Patient described in case 15. Exophthalmic goiter with moderate exophthalmos, large goiter, extreme emaciation, nervousness and weakness, and pulse rate of 135 per minute.



Figs. 135 and 136.—Same patient as in Figs. 133 and 134 after 13 months' observation. Complete recovery, with disappearance of goiter, gain of $27\frac{1}{4}$ pounds and resumption of normal duties.

enlarged to the left, the sounds being somewhat more forcible than normal. The heart rate is 135 per minute. The *lungs* and *abdomen* are negative. The *reflexes* are accentuated, and *tremor* is characteristic.

Psychic Condition: The patient is entirely rational and highly intelligent, eager to coöperate faithfully with efforts in her behalf, her main thought being to get well and go back to college. She does not present to any degree the exceedingly quickened cerebration so commonly present in these patients.

Laboratory Data: Basal metabolism is + 64; quinin test is positive.

Diagnosis: Graves' disease in which infections are the probable exciting cause. The thyroid hyperplasia was superimposed upon a preexisting simple hypertrophy.

Course Under Treatment: The patient being in exceedingly delicate health, it was necessary to adopt extreme measures in treatment, especially in the matter of rest. Coöperation was perfect, and in the course of several weeks the patient was permitted a respite from rest in bed. This was gradually increased during the ensuing month or two until she became an ambulatory case. At the termination of 7 months of treatment, the patient weighed 116 $\frac{1}{4}$ pounds, a gain of 27 $\frac{1}{4}$ pounds; the pulse was 84, and the circumference of the neck was reduced by $\frac{3}{8}$ of an inch which brought the appearance down to normal. She expressed herself as feeling perfectly well and ready at any time to resume college work. She was warned against her ambitions, however, for yet awhile, and treatment was continued for 6 months longer. At this time, her subjective and objective condition was such that she was virtually discharged from active treatment, and permitted to substitute at public school teaching. She was now placed under passive observation and is enjoying unprecedented health.

Summary: A young woman of 22, suffering with Graves' disease of rather severe type, was completely restored to subjective and objective health and usefulness at the termination of 13 months of active treatment. The thyroid gland, which was of doubtful pathology, was restored to normal.

CASE 16, age 51, housewife, referred for treatment October 18, 1920.

Chief Complaints: Weakness, palpitation, sweating, insomnia, irritability, hysteria, and attacks of diarrhea. Duration of illness 18 months.

Family History: Mother died of tuberculosis at 38; father died of typhoid at 56; otherwise family history is negative.

Previous Medical History: The patient claims never to have been sick prior to present illness.

Social and Personal History: Menstruation began at 14; married 35 years; had 10 children, 7 of whom are living and well; one child died of pneumonia, one of convulsions in infancy, and one died of unknown causes during infancy. There were no miscarriages. The patient's social environments are entirely congenial. Personal and dietary habits are good.

Present Illness: Eighteen months ago the patient began to complain of weakness, failing appetite, loss of weight, and indigestion. In course of time palpitation, nervousness, and uncontrollable irritability developed. Soon spells of hysteria were added to the clinical picture. Shortness of breath, sweating, insomnia, diarrhea, and polyuria developed recently, so that she has become entirely helpless. She had been attended by many doctors and had tried patent medicines, one of which she is taking at present. Prior to the onset of her illness, she weighed 216 pounds; she has lost 86 pounds since the onset of her complaints.

Physical Examination: The patient is a white, poorly nourished woman,



FIG. 137.—Patient described in case 16, two years prior to onset of exophthalmic goiter (enlargement of tiny snapshot).



FIG. 138.—Same person after onset of exophthalmic goiter with moderate sized goiter but without exophthalmos. Weakness amounting to almost exhaustion, marked emaciation, heart rate 128 per minute with arrhythmia.



FIG. 139.—Same patient as in Fig. 138 after 14 months of treatment. Perfect recovery with disappearance of goiter and return of strength and usefulness. Heart rate is 72 per minute, and there is a gain of 63 pounds in weight.

5 feet 7 inches tall, weighing 130 pounds. She appears anxious and helpless, and is so weak that she can hardly stand without assistance. The skin is thin, warm and moist; dermographia is easily elicited. The teeth are in poor condition, and there is pyorrhea alveolaris. The tonsils are negative. The eyes are negative except for the presence of an imperfect von Graefe sign. The thyroid is moderately swollen and atypically hyperplastic, presenting an admixture of hypertrophic changes; the greatest circumference of the neck is $14\frac{1}{2}$ inches. The lungs are emphysematous; the heart is enlarged to the anterior axillary line, presenting evidences of moderate myocardial degeneration; heart sounds are weaker than normal, and there is considerable arrhythmia. The heart rate is 128 per minute. The abdomen presents signs of visceral ptosis. The reflexes are normal; tremor is coarser than normal and distributed throughout the voluntary muscular system.

Psychic Condition: The patient is entirely rational, but very much depressed, feeling that she has but a short time to live.

Laboratory Data confirm the diagnosis of moderately severe Graves' disease of progressive course. Basal metabolism +45; quinin test positive.

Diagnosis: Graves' disease occurring insidiously, with accentuated circulatory and muscular phenomena. The exciting cause was undiscoverable.

Course Under Treatment: Because of whole-hearted co-operation, the patient's progress was most satisfactory. Each week brought increased strength and morale to the patient. Four months after the institution of treatment there was a gain of 10 pounds in weight, and the heart action was entirely regular and rhythmical, with a rate of 70 per minute. At this point the patient discontinued her visits. She wrote me stating that she was getting along splendidly, and that because of the men folk at home being out of work, she felt it was best to discontinue treatment for a while. She stated, however, that she would continue obeying instructions in the meanwhile. Seven months later, when she returned for further treatment, there was an added increase of 20 pounds in weight and a complete transformation in her appearance. After six months more of observation, the patient was discharged cured; her weight was 193 pounds, heart action normal, thyroid normal, basal metabolism was minus 5, and she resumed her household duties.

Summary: A woman of 51 with Graves' disease and cardiac arrhythmia was restored to normal after 14 months of treatment, during 7 months of which the patient had discontinued her visits to my office. When she was discharged there was a gain of 63 pounds in weight, normal heart rate and action, the thyroid was normal, and there was complete restoration of strength and usefulness.

CASE 17, age 74, referred for treatment September 18, 1919.

Chief Complaints: Extreme weakness, precordial distress, bulging eyes, goiter, sweating, and insomnia. Duration of illness approximately 2 years.

Family History is negative.

Previous Medical History: The patient does not recall having suffered with any previous illnesses.

Social and Personal History: She has been a widow 8 years. She has 4 children living and well. One son died in an accident; one died at birth during forceps delivery. Menopause occurred at 35. Her dietary habits are irreproachable. She lives in solitude and poverty because she has been abandoned by her children. She also states that she had a modest sum of



FIG. 140.—Person described in case 17 about 5 years prior to onset of exophthalmic goiter.



FIG. 141.—Same person as in Fig. 140 with severe exophthalmic goiter of 2 years' duration. She is 74 years old in this picture, and the syndrome has weakened her to the extent that she cannot walk without assistance. Extreme exophthalmos; moderate swelling of isthmus of thyroid; heart irregular and arrhythmical with pulse rate of 130 per minute; weight 94½ pounds.



FIG. 142.—Same patient after 12 months of treatment. Though she is 75 years old, she feels strong and happy; there is a disappearance of exophthalmos and goiter, pulse rate is 72, and there is a gain of 43½ pounds in weight.

money which would have kept her comfortable, but she was deprived of it by her children.

Present Illness: The patient's symptoms began about 2 years ago, and were precipitated by her children's indifference to her and her needs. She began suffering with nervousness, trembling, pain over the heart, soreness in the eyes, choking sensations in the throat, and occasional nausea and vomiting. Later, diarrhea occurred in paroxysms, with occasionally blood in the stools. There were frequent attacks of epistaxis, dyspnea on the slightest exertion, troublesome nocturia, extreme hyperhidrosis, and very marked loss in weight. The patient claims that prior to the onset of her illness she weighed about 170 pounds. She now weighs 94½ pounds. She is so weak that she is assisted into my office by two neighbors. Walking is difficult, and when an attempt is made, she appears as though intoxicated. Added to the above symptomatology, insomnia is complete; the patient claims to have been awake every night for a year.

Physical Examination: The patient is a white female, 5 feet 4 inches in height, weighing 94½ pounds. She is extremely weak, and is hardly able to walk from exhaustion. The facies present the startling expression of advanced Graves' disease. The skin is thin, moist, and very much wrinkled from senility. Dermographia is easily obtainable and is durable. The teeth are artificial. The tonsils are chronically inflamed. The eyes are extremely exophthalmic, the right eye more so than the left; all the characteristic eye signs are present. There is chronic follicular conjunctivitis and marked epiphora. The thyroid is moderately swollen, presenting a hyperplastic thickening of the isthmus. On palpation, there is a slight thrill, and on auscultation a bruit is present. The heart is moderately enlarged, presenting evidences of degeneration, but there is complete compensation. The heart sounds are weaker than normal, and there is a distinct arrhythmia tending toward auricular fibrillation. The heart rate is 130 per minute. The lungs are practically negative. The abdomen and limbs present nothing of importance. Reflexes are hyperacute. Tremor is quite typical, though coarser than normal, and universally distributed throughout the limbs and trunk.

Psychic Condition: The patient presents a picture of complete helplessness of old age, upon which there is superimposed a severe overwhelming attack of the syndrome of Graves' disease. She is entirely rational, fairly intelligent, and apparently resigned to what appears to be the inevitable fate which is awaiting her. Despite all this, she asks whether there is any hope, and pleads for some assistance.

Laboratory Data: Basal metabolism + 58; quinin test positive; carbohydrate tolerance moderately reduced.

Diagnosis: Graves' disease of severe form.

Course Under Treatment: Though coöperation could not be obtained because of the extreme social and financial obstacles (the patient being unable to purchase even the necessary drugs and food), it was soon evident that others interested in her welfare were willing to lend a helping hand. Within 6 months the patient was well on the way to recovery. There was a gain of 15 pounds in weight, a restoration of the rhythm of the heart, its rate now being not above 80 per minute, and a surprising sense of well being. At this time she was taken with a sudden attack of acute appendicitis. It was extremely difficult to convince her that operation was imperative, but when informed that unless the appendix were removed she would die within a few days, she reluctantly consented. Appendectomy was performed just in time, as the appendix was about to undergo suppuration. The patient made an uneventful recovery, returning to her home two weeks

later. From that time on, general progress was satisfactory. Barring an occasional attack of mild influenza and an occasional cold, progress was continuous, and at the termination of a year of treatment, the patient weighed 138 pounds, a gain of $43\frac{1}{2}$ pounds; the heart rate and action were entirely normal, and the patient appeared and acted no older than a woman of 60. When I last saw her, she was hale and hearty at 78, completely recovered subjectively and objectively from the Graves' syndrome as is evidenced by the appended illustration. Basal metabolism at this time was plus 2.

Summary: A woman of 74 with advanced Graves' disease and extreme asthenia, was restored to complete health, with a gain of $43\frac{1}{2}$ pounds in weight, within 12 months of nonsurgical treatment, at which time she was discharged and placed under passive observation.

CASE 18, age 32, married, printer, referred September 20, 1920.

Chief Complaints: Great weakness, palpitation and goiter. Duration of illness is about 30 months.

Family History: His father is living and well at 70; his mother is living and well at 68; he has a brother and sister living and well. He had a sister who died of tuberculosis at 19.

Previous Medical History: The patient had the usual diseases of childhood; at 11 he had a mastoidectomy performed; at 13 he had pneumonia.

Social and Personal History: He married 8 years ago and has 2 children. He states that his home environments are congenial. He is very fond of meats and takes alcoholic beverages and tobacco moderately.

Present Illness: In January, 1918, while employed as inspector in a government munitions plant, a freight train jumped the track and landed into a warehouse of shells and shrapnel. Though he was unhurt, the explosions which followed so shocked him that he fell to the floor in a faint. Several days afterwards it was discovered that his eyes were staring, and his neck was rather swollen. Gradually there developed palpitation, dyspnea, anorexia, hyperhidrosis, and great weakness. In the course of several months there was great loss in weight, goiter, marked bulging of the eyes, spells of nausea, vomiting and diarrhea, and complete insomnia. A few months ago, a physician injected a solution of quinin and urea hydrochlorid into the goiter, which, according to the patient, made him "go to pieces."

Physical Examination: The patient is a white male adult, 5 feet $7\frac{1}{2}$ inches tall, weighing 108 pounds. He appeared so desperately ill and his heart was so rapid and irregular, that I urged his wife to take him home (about 20 miles from Philadelphia) after a few preliminary observations and instructions. The subsequent examination (4 days later) revealed the following features: The skin is moist and erythematous, and covered with an acneform eruption; dermographia is easily elicited. The teeth are in fair condition. The tonsils are chronically inflamed and cryptic. The eyes are markedly exophthalmic, and all the eye signs of exophthalmic goiter are present. The thyroid is rather large and throbbing, the greatest circumference of the neck being 17 inches. Palpation over the thyroid reveals the typical thrill, and on auscultation there is a loud systolic and diastolic murmur. The heart is tremendously enlarged extending over to the left axillary space; its action is so tumultuous that the entire body seems to vibrate with its cycles. The apex beat is markedly diffused, and all the superficial vessels of the body, but especially those of the neck, are throbbing violently. On palpation there is a heaving of the entire chest with cardiac cycles. Auscultation presents auricular fibrillation, in which the



FIG. 143.—Person described in case 18, about 3 years prior to onset of exophthalmic goiter (enlargement from a small snapshot in possession of patient).



FIG. 144.—Same person with a very severe type of exophthalmic goiter. Dyspnea is so marked that he is gasping for breath. There are extreme exophthalmos, large pulsating goiter, auricular fibrillation, pulse rate approximately 200 per minute, tremor of entire body with choreiform movements of arms and legs, and a reduction in weight to 108 pounds.



FIG. 145.—Same patient as in Fig. 144 after 3 weeks of treatment. Note changed expression and a gain of 16% pounds in weight.



FIG. 146.—Same patient 7 months after the institution of treatment. Recovery with disappearance of exophthalmos and goiter. The heart action is normal, pulse rate 72 per minute, there is a gain of 25 $\frac{1}{4}$ pounds in weight, and patient has returned to work.

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pulse deficit is perhaps 100 or more. The pulse rate, as far as can be determined, is somewhere about 200 per minute. The *lungs*, *abdomen*, and *limbs* are practically negative. The *reflexes* are markedly exaggerated, and the *tremor* is distributed throughout the body. In fact, there is an admixture of the tremor of Graves' disease, of choreiform movements, and of the vibrations of the turbulent heart.

Psychic Condition: The patient is extremely toxic, and is unable to sit still. There is a shrug of one shoulder and a twist of the other, now a kick of a leg, and then a wild motion of an arm—the purposeless incoördinate muscular movements of a person who seems to have no control over voluntary muscular activity. Speech is slurred, hasty, and monosyllabic; the general mental attitude is one of overalertness, but extremely vacillating as to the points discussed. Despite all this, he seems rational and eager to coöperate faithfully in efforts to assist him.

Laboratory Data: Basal metabolism + 90, quinin test is positive; sugar tolerance is moderately reduced.

Diagnosis: Severe Graves' disease with myocardial degeneration.

Course Under Treatment: After due warning to the patient and his wife that strict coöperation in treatment would be the only hope for him, a regimen of treatment was outlined, and the patient was to return once every few days for observation. Three weeks later, the patient weighed 124 $\frac{3}{4}$ pounds, a gain of 16 $\frac{3}{4}$ pounds. The heart rate, now 120 per minute, was quite regular and rhythmical, all evidences of fibrillation having disappeared. In brief, there was a complete transformation in the patient's appearance and poise. Speech and actions were deliberate, and the patient expressed himself as "feeling fine." During the ensuing 4 weeks, progress was more tardy, though evident. The heart rate was 100 per minute, regular and rhythmical, the weight was 127 pounds, and the patient claimed that he felt so strong that he was desirous of returning to work. From this time on matters did not progress as well as heretofore. At each weekly visit there was evident retrogression in his condition, for there was a slight return of arrhythmia, a loss of a few pounds in weight, and a diminution in morale. Observing this status for a few weeks, I took him to task through a kind but firm "third degree" process, at the termination of which he confessed to serious indiscretions in dietary and other regulations. He also stated that he had been walking about quite a bit and ignoring instructions concerning rest. When questioned as to the why and wherefore, he finally confessed that his wife was entirely to blame, and that he had "too darn many fights at home." I urged him to realize that it takes two to make a quarrel and insisted on continued obedience to instructions, else all would be lost. He promised that he would obey faithfully this time, but two weeks later, he stopped his visits abruptly. Four months later, he again called on me. I could hardly recognize him, for he appeared entirely normal. Asked why he had absented himself, he stated that he felt so much better from treatment that he thought he was entirely well and was tired of loafing. "And besides," said he, "to go to work was the best way of keeping away from home and from fights." He also explained that he had been taking the medicine prescribed during all this time, and that he had tried to adhere as best he could to the instructions in diet. Physical examination at this time revealed a complete absence of the formerly enormous goiter, the neck being normal in size and shape; the heart rate was 72, weight 133 $\frac{1}{4}$ pounds, exophthalmos gone, and in every respect the patient had entirely recovered, presenting a basal metabolism of plus 7.

Summary: A very severe case of Graves' disease in a male adult with

auricular fibrillation, and who found it difficult to coöperate with instructions in treatment, made a phenomenal recovery within 7 months after the institution of treatment, during 4 months of which he had absented himself from observation.

CASE 19, age 45, housewife, referred by Dr. J. J. Stanton of Philadelphia, December 5, 1921.

Chief Complaints: Weakness, especially of the lower limbs, cough, restless sleep, palpitation, dyspnea, insomnia, and diarrhea. Duration of illness is about 4 years.

Family History: Her father died of asthma at 54; mother died of diabetes; patient has a daughter who is nervous.

Previous Medical History: Negative.

Social and Personal History: Menstruation began at 12 and had been regular; she married at 20; has 4 children living and well. She is very fond of meat and coffee, taking both to excess. Home environments are congenial. She had always been of a nervous temperament.

Present Illness: About 4 years ago, one of her children was afflicted with infantile paralysis. This so shocked the patient as to give rise to palpitation, restlessness, insomnia, and loss in weight. Several months later, the patient began to experience pains about the heart which became an added psychic trauma, because of the fear of sudden death from heart disease. Shortly afterward, the heart pains became so severe as to take the form of angina pectoris, often occurring in the middle of the night and necessitating a call of the family physician for the purpose of relieving her with a hypodermic of morphine. The cardiac manifestations and the attacks of angina became more severe and constant as the disease progressed, and nervousness became associated with hysterical outbursts. Exophthalmos soon became evident, giving the patient the appearance of perpetual fright and anxiety. Trembling, subjective and objective, became generalized, and both patient and relatives feared that the end was near. Her weight prior to illness was 170 pounds, now it is 122 $\frac{3}{4}$ pounds.

Physical Examination: Patient is a white, dark-complexioned woman, 5 feet 3 $\frac{1}{2}$ inches in height, weighing 122 $\frac{3}{4}$ pounds. She is so weak that she could hardly wait to fall into a chair to rest herself. The anticipation of special observation seems to bring on an exaggeration of the trembling, the exophthalmos, and the diaphoresis. The skin is dark, thin, and very moist, and there is marked dermographia. The teeth are in poor condition, with evidence of pyorrhea. The tonsils are moderately congested and infected. The eyes are markedly exophthalmic; the Dalrymple, von Graefe and other eye signs are present; there is a moderate degree of follicular conjunctivitis. The thyroid presents moderate, diffuse, hyperplastic swelling; it throbs, presents a thrill, and the characteristic bruit which is both systolic and diastolic. The greatest circumference of the neck is 13 $\frac{1}{2}$ inches. Heart is hypertrophied, the left border extending to within the anterior axillary line, and downward to the sixth interspace. The heart sounds are somewhat weaker than normal, the first apical sound being prolonged into a soft, blowing murmur transmitted into the left axillary space. There is an accentuation of the second pulmonic sound. There is an occasional intermittency with a tendency toward gallop rhythm. The heart rate is 150. The lungs present slight congestion posteriorly over both bases. Otherwise they are negative. The abdomen presents a moderate tendency toward visceral ptosis, and there is some tympanites. The limbs are negative. The reflexes are considerably

heightened. *Tremor* is extreme and universally distributed throughout the body.

Psychic Condition: The patient is continuously asking whether there is serious heart disease and whether she is in danger of sudden death. There is hasty, slurring speech, accelerated ideation, and the sudden purposeless, choreiform movements so commonly observed in advanced Graves' disease. The patient appears virtually "seared to death" of her future, and promises to coöperate most faithfully in obedience to instructions in treatment.

Laboratory Data: Basal metabolism +70; quinin test is positive; sugar tolerance is moderately reduced.

Diagnosis: Advanced Graves' disease with myocardial degeneration.



FIG. 147.—Patient described in case 19. Exophthalmic goiter of 4 years' duration with marked circulatory and nervous phenomena and attacks of angina pectoris. She has been confined as an invalid for over a year. Pulse rate 150 per minute.



FIG. 148.—Same patient as in Fig. 147, at time of discharge from treatment. Perfect recovery with disappearance of exophthalmos and goiter; the pulse rate is 72 per minute; there is a gain of 40 pounds in weight.

Course Under Treatment: Because of environmental difficulties, progress under treatment was slow and fraught with obstacles. Her living quarters were very inadequate for the large family. Inquiring curious neighbors and so-called visiting friends were keeping the patient continuously in a state of restlessness both of mind and body, and the manifest impatience of all concerned because recovery was not yet at hand at the end of the first month of treatment—these and other things required continued psychotherapeutic attention in which consultations with her husband and older children became necessary. In the course of events, however, a mental and sociological adjustment consistent with favorable progress was made possible, and the patient improved rapidly thereafter. At the termination of a year's treatment, the patient's condition was almost normal, and both she and I were looking forward to a discharge from treatment during the ensuing few months. The attacks of angina had ceased completely following the first

few weeks of treatment; insomnia was entirely overcome; the heart rhythm was normal and its rate 80 per minute, there was a gain of 17 pounds in weight; the patient appeared completely transformed to a healthy-looking individual; the thyroid gland was normal; the eyes practically normal; and subjectively, the patient felt so strong that she was eager to resume all her household duties. At this point, she stopped treatment abruptly. When she returned 6 weeks later, there was a mild exacerbation of subjective and objective symptoms. She begged to be pardoned for her sudden discontinuance and for the many indiscretions that she had committed, explaining that she had been making preparations for the marriage of her daughter which occurred in her own house, and all the responsibility and strain had fallen upon her shoulders. During her absence she had apparently forgotten that she was a patient and had released herself completely from the influence of diet, medication, and other attention. The patient was now warned unless coöperation was whole-hearted and sincere, I would refuse further treatment. This she promised faithfully, and at the termination of the ensuing 3 months (April, 1923), the patient was again subjectively and objectively normal; weight was 163 pounds; pulse rate was 72; and she was discharged from active treatment. She was now placed under passive observation to report once a month during the ensuing year.

Summary: A female patient of 45 with advanced Graves' disease of about 4 years' duration, myocardial degeneration and attacks of angina pectoris was discharged after 16 months of active treatment (6 weeks of which were spent by the patient in indiscretions). When she was placed upon passive observation, there was a gain of 40 pounds in weight, a restoration of the heart, thyroid gland, eyes, nervous system and basal metabolism to normal, with complete subjective and objective recovery.

CASE 20, age 35, housewife, referred for treatment May 24, 1921.

Chief Complaints: Goiter, nervousness, restlessness, weakness, loss in weight. Duration of illness, 3 years.

Family History: Negative.

Previous Medical History: Negative.

Social and Personal History: Menstruation occurred at 14 and was always regular and normal; she married at 20, had 7 children; no miscarriages. Her home is fairly congenial. Her dietary habits are fair.

Present Illness began 3 years ago, following the funeral of a dear friend, at which time she fainted. Shortly after this incident, she became weak and nervous. She was troubled with palpitation, shortness in breath, headache, indigestion, restless sleep, and sweating. Goiter began to develop 18 months ago, and bulging of the eyes, first one eye and later the other, about 12 months ago.

Physical Examination: The patient is a white female, 5 feet 6 inches tall, weighing 129 $\frac{3}{4}$ pounds, presenting the usual facies of Graves' disease. The skin is soft and moist; dermographia is easily elicited and is very marked. The teeth are in very poor condition, and there is pyorrhœa alveolaris. The tonsils present moderate chronic inflammation. The eyes are moderately exophthalmic, the left eye more than the right; all the other eye signs typical of Graves' disease are present. The thyroid is moderately enlarged, presenting the physical signs of hyperplasia; there is a thrill on palpation and a bruit on auscultation. The greatest circumference of neck is 14 $\frac{5}{8}$ inches. Heart: left border extends to a half inch outside the midclavicular line, the sounds are violent and heaving, the rate is 120; the heart action is regular and rhythmical. The lungs and abdomen are negative.

Reflexes are hyperactive. *Tremor* is very typical and is characteristic of the entire voluntary muscular system.

Psychic Condition: Patient is entirely rational, though rather impulsive and quick in ideation, and somewhat choreiform in muscular movements. Emotionalism is evidenced by the shedding of a few tears now and then when mentioning the death of her dear friend 3 years before.

Laboratory Data: Basal metabolism is plus 58; quinin test is positive; sugar tolerance is below normal.

Diagnosis: Progressive Graves' disease of 3 years' duration, induced by the psychic trauma incident to the death of a dear friend.

Course Under Treatment: Though the patient was willing and anxious to coöperate in all the details of treatment, she was not in position to do so



FIG. 149.—Patient described in case 20. Exophthalmic goiter of 3 years' duration with marked asymmetry of exophthalmos; pulse rate 120 per minute.



FIG. 150.—Same patient as in Fig. 149, at time of discharge from treatment. Perfect recovery, with reduction in circumference of neck by 1½ inches and disappearance of goiter; disappearance of exophthalmos, pulse rate is 72 per minute, and there is a gain of 35½ pounds in weight.

to any considerable extent because of her large family, her youngest child being but an infant and requiring constant attention. Furthermore, she could not afford the expense of a servant excepting someone to do her washing. Despite these obstacles, however, progress though slow was continuous, and in course of 6 months the patient expressed herself as "feeling fine." There was a gain of 22 pounds in weight; the pulse was normal; eyes and thyroid were nearly normal, and she was well on her way to recovery. At this time I insisted upon the removal of her infected teeth, and her dentist proceeded so to do. Following the dental operations, there was a moderate relapse of symptoms, but within several weeks the patient was again in excellent health. At the termination of a year's treatment the patient weighed 165 pounds; there was a complete disappearance of goiter, so that her neck was entirely normal, its circumference being 13½ inches; eyes,

heart rate and basal metabolism were normal, and the patient expressed herself as never having felt so well in her life. She was now discharged from active treatment.

Summary: A woman of 35 with typical progressive Graves' disease of 3 years' duration was restored to complete subjective and objective health and unprecedented well being, with a gain of 35 $\frac{1}{4}$ pounds in weight at the termination of 12 months of active treatment.

PERMANENCY OF NONSURGICAL RECOVERY FROM EXOPHTHALMIC GOITER

In patients discharged from a régime of treatment as herein outlined relapse is highly improbable. *I have never had an instance of relapse in patients who have continued treatment until formally discharged.* Such an individual, mentally and physically transformed into a more stolid being, is quite as insusceptible to Graves' disease as the average person not predisposed to this affection.

Incidents which could formerly serve as exciting causes of Graves' disease are now laughed away as trifles. This is exemplified in Case 14 in the details of the course under treatment. In Case 15 the following incident was recently reported to me: The grandmother and a small grandson were lost one afternoon, and everyone of the household was frantic with worriment. Our former patient, however, was not flustered and surprised them all by her wise counsel and collected demeanor. Again, a daughter of the patient mentioned in Case 19 developed a sudden profuse epistaxis during the night following a septal operation. The entire family became excited except our former patient, who calmly phoned the doctor, carried out his instructions, and successfully nursed the patient through the night. In the case of a recently discharged patient in Roxborough, Philadelphia, there occurred a bomb explosion at midnight within a city block of his residence. Though the house shook and several window panes were broken, and everyone else in the house was awakened in terror, our former patient was scarcely perturbed. After reassuring the other members of the family that all was well, he went peacefully back to bed as though nothing had happened.

These discharged patients are entirely different from their former selves. During the existence of the syndrome the patient was tense, excitable, "on edge"—the mental and physical processes being comparable to the quick acting trick motion picture in which the spectator becomes almost dizzy with the rapid course of events. The patient "breezed" into your office, sat down precipitously, and talked with such haste as though there were but ten rather than sixty minutes to the hour. There may have been observed choreiform movements, especially of the arms, legs and shoulders, indicating an impatience with time itself. There was no such thing as sitting quietly in passive attitude. There was, in brief, a quickening of all the conscious and unconscious activi-

ties with an equivalent reduction in the threshold of nervous and more especially emotional reaction.

But now, as the result of physical and mental guidance of the physician for a year or longer, the discharged patient acts and thinks entirely differently from his former self. He is now cool, calm, and collected in thought and action. Sitting down, arising, walking, talking, thinking, all this is done with the deliberation of one who is accustomed to calculate every intention and action. There is a poise that is remarkable to behold. There is an increase in the threshold of reflex and emotional response, the most vital requirement for permanency of recovery from this disease. Thus the subject, taught to live in accordance with what I term an *anti-Graves' disease existence*, is now changed into an individual of maximum longevity and of usefulness to self and society,—an example of equanimity that is not uncommonly an object lesson to the doctor himself.

CHAPTER XXVIII

CONCLUSIONS ON THE NONSURGICAL MANAGEMENT OF EXOPHTHALMIC GOITER

AS WE survey the periods in medicine, we find repeated examples of theories and procedures formerly considered proper, giving way to other theories and procedures in accordance with advances in physiological and clinical observation. Arts and sciences, as well as men, are susceptible to ruts or fads into which they will fall and remain for a much longer period than subsequent developments and conditions justify, simply because it is a somewhat painful procedure requiring considerable effort to come out into the open and accept views at variance with habitual methods.

The most important disease in which there is a current evolution of opinion is exophthalmic goiter. For many years the majority of medical men have considered this disease as one belonging to the operating table for relief. Many theories, ingenious and otherwise, have been promulgated to suit this therapeutic conclusion, but many thousands of patients having made what appeared to be a good operative recovery were observed still to suffer from Graves' disease. There was indeed an *operative* recovery, but what of recovery from the syndrome? That is the question and the basis of the entire argument—*recovery*—complete, permanent restoration of physical and mental health—which surgery, in the abstract, has been incapable of demonstrating.

The Pro and Con of Operative Mortality and Statistics.—A recent patient of mine had made arrangements with a prominent surgeon in Philadelphia to be operated on. Being of an analytical nature, happily married and rather fond of life, he asked: "Now, doctor, you are a good surgeon, and I will probably live through the operation. Thus far I am convinced. But will I get well of my sickness? I must be reasonably certain of this before I enter the hospital." The surgeon, an honest, frank gentleman, informed him that statistics show a large percentage of improvement, but as to complete recovery, time only can tell. "If you cannot give me more assurance than that, and if you cannot show me surgical cures of my sickness, you shall not operate on me!" He left the surgeon, applied for nonsurgical treatment, and after three months of such management he was rapidly becoming a normal individual. All evidences of the former typical Graves' disease were gone excepting a still very slight exophthalmos in one eye. Three

months later, he was in perfect physical condition and returned to business. This is one of innumerable similar instances that could be cited—cases restored to health, happiness, usefulness, and normal longevity *without surgery*.

Though on the offensive with respect to operative mortality and immediate clinical results in Graves' disease, surgery is now assuming the defensive with respect to justification of operative procedures and the completeness and permanence of recovery. It is the prolonged and still unsettled contention between the various schools of treatment and the scarcity of clinicians who understand the disease and its victim that render the treatment of such a patient an apparently unmanageable task.

Sajous is quite direct when he states that "The average physician thinks only of the operative mortality of Kocher, the Mayos and other equally efficient operators, which operative mortality has become virtually *nil*. But the ultimate results even in such hands tell a different story. Judd and Pemberton, of the Mayo Clinic, for instance, give 45 per cent as the proportion cured eight years after operation. Stark, reviewing the final results of several prominent German surgeons, places the cures at approximately 30 percent. Unfortunately, while there are throughout the country other surgeons of first order, the majority cannot conscientiously be so graded. Operative mortality grows apace with deficiency of operative skill and knowledge and to place it at 6 per cent., and the ultimate results, say after four years, at 18 per cent cures, is to be generous to the average surgeon. . . . After partial thyroidectomy, it means continued excitation of the portion of the organ left *in situ*, and in the majority, only 'improvement,' a condition far removed from 'cure,' judging from cases I have had to treat. If too much glandular tissue is removed, a condition worse than myxedema—again speaking of operated cases that have drifted my way—is the remote result."

The low operative mortality rate in exophthalmic goiter, in perfectly appointed clinics, is *surgically fortunate*. *Clinically*, it is unfortunate, in that its coercive influence causes hopeful patients and many hopeful busy practitioners to put a blind faith in the knife as a remedial measure in this disease. Improvement in surgical technic and a lowering of operative mortality rate are not *per se* good reasons for operating. The *rationale* of thyroidectomy should not be based upon the fact that only two or three in a hundred die of the operation. It is not justified even if many patients surviving operation are improved, if this amelioration of symptoms is incomplete and temporary. The patient rightfully expects but one result for the risk undergone and the resulting scar, and that is an unequivocal *cure*—a complete, permanent, subjective and objective restoration to health, happiness and utility. Moreover, the mortality rate, were a broadcast average taken, is still

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genuinely high. Thyroidectomy of the hyperplastic thyroid is replete with peril and is one of the most difficult and dangerous of surgical procedures, the *average* mortality rate of which is considerably in excess of ten percent. In my observations I find that in clinics where thyroid work is merely incidental to general surgery, a fifty percent. mortality in Graves' disease is occasionally met with. Even in ligations, death occurs when it is least expected. If it is true that "a patient dead is 100 per cent dead," we begin to dread lest in the very next patient scheduled for thyroidectomy something goes wrong.

In addition to the mortality rate, statistical figures in the surgical management of exophthalmic goiter include a consideration of clinical results. A survey of statistical sheets from various institutions reveals an interesting fact, namely, the use of terms vague in their implications. The columns of figures of percentages in each instance are embellished by such indefinite terms as "slightly improved," "markedly improved," and "cured." No mention is made of patients whose condition is aggravated through the operative procedure—a common cause of post-operative death; in other words, there is no consideration of acute exacerbations with fatal termination, hours, days or weeks after operative procedure. These fatalities are not, but should be included in the mortality rate. The percentage of unimproved cases requires no comment, except that this probably includes patients made worse by the operation. With regard to slightly improved and markedly improved cases, it might be said that not only are these terms extremely elastic, depending upon the personal equation of both patient and surgeon, but their very vagueness stamps them as illogical concepts. What is the dividing line between unimproved and slightly improved? Between slightly improved and markedly improved? Is it the eyes? The heart? The nervous system? The goiter? The body weight? The eyes, even in the presence elsewhere of marked temporary improvement following thyroidectomy, rarely, if ever, improve to a perceptible degree. While the internist admits that removal of a considerable portion of the hyperplastic thyroid in many instances reduces the thyroid toxemia, resulting in improvement with regard to the heart rate, the nervous system, and the body weight, this amelioration of varying degree occurs less often than statistics indicate and is short lived, its duration depending upon the rapidity of the process of overwhelming compensatory hyperplasia of the remaining portion of the thyroid gland. Thus the patient, though happily improved, say to the extent of approximately fifty percent., with a corresponding return of usefulness to self and society, in course of time (usually within several months), experiences a gradual return, subjectively and objectively, of the syndrome for which operation was performed, and the doctor is again consulted. How often do we find this patient the subject of repeated surgical procedures! Again, how often do we find this individual, after having visited in-

numerable doctors' offices and clinics, disgusted with the medical profession and resigned perforce to the inexorable course of the disease? And again, after having made a good *operative* recovery, how often is the patient in course of time a victim of myxedema, permanent impairment or loss of voice, damage to or removal of the parathyroid substance, and other surgical misfortunes!

The Uncertainty of Surgery.—The *multiplicity* of operations, regarded by surgeons as necessary in a goodly percentage of patients, is not only an added peril to life, but diminishes the prospects of final recovery. In a recent paper Mayo and Boothby make the following significant remarks: "The most disturbing factor from the surgical point of view is the ease and unexpectedness with which a so-called postoperative acute thyroid crisis is initiated, to which the patient often succumbs in from eighteen to thirty-six hours. During 1922, ligations or thyroidectomy were performed on 633 patients with exophthalmic goiter. On this basis, the mortality rate from eleven deaths is 1.74 percent. While this is a true mortality rate, so far as it can be determined for this group of patients at the present time, yet it must be emphasized that some of the patients will come to further operative procedures during the next year, and that surgical procedures were started on certain others during the previous year. Therefore, this percentage cannot be considered as representing a final mortality rate by cases." Multiplicity of operation is dependent upon clinical relapse, but the surgeon usually ascribes its need to lack of "subtotality" of the original thyroidectomy. That the thyroid substance left by the surgeon sooner or later increases in size by cellular proliferation until there is again a fair-sized goiter, is seen not only clinically and in the postmortem room, but is proved through animal experimentation. Leo Loeb, for instance, confirming the results of Halsted's experiments, found that after the subtotal extirpation of the thyroid in guinea pigs, the remainder of the gland showed hypertrophy in course of time. The piece of hyperplastic thyroid tissue left *in situ* still hyperfunctionates—still heeds the call of the uninfluenced, activating etiological factors which require the assistance of an *entire* thyroid gland for compensation, and soon again this organ endeavors to become entire again through regenerating proliferating processes. Often the regenerated thyroid mass exceeds in size the dimensions attained before operation, when the surgeon again feels "in duty bound" to operate. Surgical attack of the hyperplastic thyroid is physiologically, pathologically and clinically inconsistent. It is the almost unanimous opinion of endocrinologists throughout the world, that though the disease asserts itself partly as a thyrotoxemia because of thyroid hyperactivity, the direct pathogenesis is of *pluriglandular* nature, the thyroid hyperactivity occurring merely as a link in the chain of events in which the thymus, suprarenals, pituitary, parathyroids, pancreas, and gonads play no small part. In brief, Graves' disease is a

generalized neuro-endocrine dysfunction, in which thyroid hypersecretion plays its part not causally, but sequentially. Thyroid hypersecretion is no more the main factor in the clinical picture of this affection than is splenic hypertrophy of typhoid fever the main factor in typhoid. The hyperactivity of the thyroid, whether the organ be enlarged or no, and the enlarged spleen, are results, not causes of their respective afflictions. Each is a *constituent* of the syndrome of which it forms a part, and it is just as irrational for surgery to attack the thyroid in Graves' disease as it is to attack the spleen in typhoid fever.

The thyroid responds to physiological demands, increasing in size and function during puberty, adolescence, pregnancy, and the menopause. Again, the thyroid responds to pathological demands made upon it by infections, focal and general, psychic trauma, and glandular disturbances elsewhere in the body, frequently resulting in a decided increase in size and structure of the organ. In each case the organ performs an important duty, that of defending itself against irritating influences and dysfunction elsewhere, and in this defense the element of compensating hypertrophy and hyperplasia in the interests of bodily integrity is vital. It is just as absurd surgically to attack this compensating protecting organ during pathological demands as it is to operate on it because of the physiological demands.

How much or how little gland to leave *in situ* during thyroidectomy has long been and still is a surgical controversy. For fear that the removal of too much thyroid will result in hypothyroidism and the removal of too little in the need for another operation, surgeons have begun to employ figures with respect to how much of the gland is to be permitted to remain. Some state that one-sixth of the gland should be left behind, others one-fifth, still others one-third, and occasionally an opinion is advanced stating dogmatically that not more than one-eighth of the gland should be left behind lest there be a recurrence. All claim that some of it must be left behind, thus admitting that the gland is a vital organ (thanks to the experience of men who formerly removed the entire gland). Do such controversies arise with respect to how much of the tonsils or of the appendix should be left behind?

Irrelevant Analogies of Surgery.—The surgeon occasionally asks: "Why remove diseased tonsils, and fear to remove a diseased thyroid?" Remove all of a diseased tonsil, and the operation is complete and satisfactory; leave a part and we are in course of time confronted with the need for another operation, the remaining portion having served as a root for the regeneration of the removed tissue. Remove the thyroid, however, and the patient is ruined or killed through the resulting myxedema. Leave a portion in order to conserve the life of the patient, and as the lingering portion of diseased tonsil, sooner or later the entire gland is regenerated, and we have again a full fledged example of hyperplastic thyroid. Again, "Why remove a diseased appendix," the

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surgeon argues, "and hesitate to remove a diseased thyroid?" The analogy is erroneous for (1) appendicitis is a local disease while Graves' disease has a widespread etiology, symptomatology, and physiologic relationship; (2) the appendix is a vestigial organ while the thyroid is a vital organ and must not be tampered with; (3) the appendix, in appendicitis, is the seat of germ activity while the hyperplastic thyroid is not infected; (4) operative removal of the appendix renders the patient well and healthier than ever, while the total removal of the thyroid means a slow death from cachexia strumipriva and partial removal does not cure exophthalmic goiter. It is obvious that, logically speaking, the surgeon is on the horns of a dilemma.

Is surgery ever indicated in Graves' disease? Yes, just as surgery is occasionally indicated in such medical conditions as typhoid fever in case peritonitis develops; in scarlet fever, in the event of otitis media; or in pneumonia, in case of a complicating empyema. In Graves' disease, surgery is indicated when (1) marked pressure symptoms of cervical and thoracic structures are evident; (2) malignant degeneration of the thyroid occurs (marked pressure symptoms and malignancy are unusual occurrences during the course of thyroid hyperplasia); (3) a local structure (tonsils, appendix, pelvic abnormalities) which, by a careful process of exclusion, is found to have an etiological bearing on the syndrome. Surgical removal of infectious foci, in breaking the continuity of the vicious circles upon which the symptom complex depends, may bring about a cure.

But I hear a disapproving surgeon say: "Surgery *does* cure exophthalmic goiter, for I have seen many examples of it." Quite true, but on analysis, these "cures" by thyroidectomy may be explained by the following:

(A) Careful, open-minded surgeons, when confronted, with a case of Graves' disease, subject the patient to prolonged preoperative and post-operative nonsurgical treatment. A cessation of expert postoperative nonsurgical measures in a case of this sort (measures not synonymous with the mere administration of quinin hydrobromid) would prove the futility of surgery. Such a patient having recovered from the immediate surgical shock may, in the absence of surgical accidents, even make a complete clinical recovery, not because of, but in spite of surgery. Here it is evident that the credit reverts not to surgical but to nonsurgical management of the disease, which latter alone, if carefully applied, is capable of curing Graves' disease. This opinion is confirmed by surgeons themselves, who agree that without a carefully outlined postoperative treatment of indefinite duration, the surgical procedure is a flat failure. As an illustration, Crotti states: "When once a patient has been operated on, he becomes again a *medical patient*. He should be followed medically until cure is assured. The same medical principles which apply prior to the operation find their indication and use-

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fulness after the operation: rest, change of environment, automobiling, sojourn in mountainous regions, are the best adjuvants of the surgical treatment." To exemplify further, in Ochsner's clinic the following list of printed directions is given to each discharged patient:

"1. You should avoid all excitement or irritation like attending receptions, shopping, church work, or politics.

"2. You should get an abundance of rest by going to bed early and taking a nap after luncheon.

"3. You should have an abundance of fresh air at night, consequently you should sleep with wide open windows or on a sleeping-porch.

"4. You should eat and drink nothing that irritates the nervous system, like tea, coffee, or alcohol. Of course you should not use tobacco in any way.

"5. You should eat very little meat. If you are very fond of meat, take a little beef, mutton, or breast of chicken, or fresh fish once or twice a week or at most three times a week.

"6. You should drink a great deal of milk or eat things that are prepared with milk, such as milk soup, milk toast, etc.; cream and buttermilk are especially good for you.

"7. You should avoid beef soup or beef tea or any kind of meat broths.

"8. You should eat an abundance of cooked fruits and cooked vegetables or very ripe raw fruits, or drink fruit juices prepared out of ripe fruits.

"9. You may eat eggs, bread, butter, toast, rice, cereals.

"10. You should drink an abundance of good drinking water, or if this is not available, you should boil your drinking water for 20 minutes, or drink distilled water."

Ochsner states that with the exception of a very small number of cases in which an insufficient amount of the gland had been previously removed or in which the remnant left at the primary operation had increased in size, in practically all of the cases which had recurred, almost invariably it was found that the patients had disregarded the above directions regarding diet, rest, and hygiene following their operative treatment, or they had been permitted to return to their homes without definite instructions in this direction. Is not this an outspoken confession of the failure of surgery in exophthalmic goiter? Note that the real basis of relief is frankly stated to be the above mentioned nonsurgical procedure without which surgery is admittedly a failure. These rules alone, properly carried out (and this is not refuted by thyroid surgeons), are capable of curing all coöperative patients who still have a reasonable amount of recuperative power.

(B) Occasionally a subject of Graves' disease is completely and permanently cured, not by thyroidectomy, but by the removal of an infected focus. The surgeon who is at the same time an endocrinologist and a diagnostician will, by painstaking efforts, seek to discover, and frequently find that the exciting factor in the production of the syndrome and its various vicious circles is infected tonsils, a uterine neoplasm, a chronic appendicitis, or the like, the removal of which

spells cure. Sir Arbuthnot Lane, for instance, reports a case in a young girl completely cured by the removal of an offending portion of the large intestine. The internist cannot but concur with the opinion of clinicians of such scientific stamina, for these make sure of their grounds before proceeding. Such are undeniably genuine instances of surgical cure of Graves' disease, but the thyroid gland and its environs are undisturbed.

(C) It is well known that in rare instances cases tend toward spontaneous recovery.¹ A patient of this sort, in recovering after a thyroideectomy, has Nature to thank and not surgery. It must be borne in mind, however, that these instances are so rare that it is safest to deem spontaneous recovery a negligible element in the course and prognosis of Graves' disease.

(D) The "Basedowified" type of goiter or toxic adenoma, *i.e.*, those instances in which, superimposed upon a long standing simple or non-toxic goiter, there occurs a kind of Basedowian syndrome, should not be regarded as Graves' disease, for the removal of the old goiter will cause the syndrome to disappear and will cure the patient. This class of patients is the largest source of statistical figures of so-called markedly improved and cured cases of Graves' disease. The still prevailing looseness of terminology in which the terms "toxic goiter" and "hyperthyroidism" are made to include both toxic adenoma and Graves' disease, and the lack of discrimination between these two totally different affections are still largely responsible for the chaotic state of the therapeutic approach existing in many quarters. Toxic adenoma, it is true, should be treated along surgical lines, not, however, without a preoperative and a postoperative course of careful nonsurgical management in order to make surgery itself eminently successful. A case of this sort is not one of genuine Graves' disease.

(E) A patient suffering from simple or nontoxic adenoma on coming into the presence of the surgeon for examination may present rapid heart,

¹ In the rare instance of asserted spontaneous recovery a return to normal of the circulatory and other structures is inconceivable. Personally, I have never seen an instance of real spontaneous recovery of undoubted Graves' disease. Yet Kessel, Lieb, and Hyman advocate the extreme policy of "skillful neglect." If this wide-spread, tissue-destroying affection is limited and self-rectifying, then we might say this of all diseases in the practice of medicine, and physicians, being mere meddlers with the processes of Nature, had better devote their time to something more useful. The advocates of "skillful neglect" have arrived at very hasty conclusions in their reports on patients under their care. Patients "restored to economic usefulness" within several weeks as a result of rest in bed may be temporarily improved, *not permanently cured*. These observers have not followed up their patients for a sufficient length of time to note the damage wrought by "skillful neglect." Internists who have been brought in intimate contact with hundreds of neglected sufferers from exophthalmic goiter would just as likely trust a patient of this sort to spontaneous recovery as to throw a person who had never learned to swim overboard into deep water and expect him to bob up smiling.

certain nervous manifestations, and even tremor, which symptoms, due to anticipation or fright, are hurriedly construed as constituting pathognomonic evidences of Graves' disease. Thyroidectomy is performed, and the patient is cured. This is a cure of nontoxic goiter, not of Graves' disease.

(F) Goiters, simple or nontoxic, which by pressure upon vessels and other structures within the neck and chest give rise to the so-called mechanical goiter heart, present a syndrome which is often confused with that of Graves' disease. It can be seen that these three types of cases, (D), (E), and (F), are instances in which the diagnosis of the surgeon is called into question. We believe these cases to belong strictly in the realm of surgery, but they should be excluded from statistics of results of treatment of Graves' disease.

(G) Some cases of Graves' disease are apparently tending toward recovery, but in reality leading slowly but surely to a state of myxedema. These constitute the so-called "burned out" thyroids, in which the thyroid hyperactivity gradually gives way to hypoactivity because of tissue degeneration within the gland. The surgeon who operates on a case of this sort during the stage of hyperactivity of the gland is placed in a peculiar predicament when some months after apparent cure in every demonstrable respect the patient is brought to him with a full fledged picture of myxedema. How can he prove to himself in order to still his conscience that he did not remove too much thyroid in this patient? In other words, he has no means of discriminating between spontaneous and postoperative cachexia strumipriva. This, by the way, is another argument against thyroid interference in cases of undoubted Graves' disease. These cases of postoperative myxedema rarely reach the surgeon's attention, as it is the internist to whom the patient applies for treatment.

Clinical Differences between Thyroidectomized and Nonthyroidectomized Patients.—Complex as may be the task of the internist in managing to a successful outcome an unoperated patient with exophthalmic goiter, the task is infinitely more difficult, though usually finally successful, in one whose thyroid has already been tampered with one or more times by surgery. The main clinical differences between the two types of patients are as follows:

1. The course of the disease in a patient surviving operation is usually more chronic, the bodily tissues becoming more firmly settled into morbid physiological function.
2. This confirmation of morbid tissue habit, asserting itself in hyperexcitability and excessive catabolism, leads to greater degenerative changes than are observed in less chronic (unoperated) patients.
3. These changes, occurring in the circulatory system, account for the numerous instances of cardiac decompensation seen in operated patients.

4. These changes often show a predilection for the central nervous system, as evidenced by the greater predominance of insanity in operated than in unoperated patients.

5. Frequently the thyroid gland itself is the site of marked post-operative degenerative changes. Many thyroidectomized patients within a few months present evidences of both hyper- and hypothyroidism, changing sooner or later to the complete clinical picture of myxedema or cachexia strumipriva.

6. Taking the foregoing factors into account, it is evident that the difficulties of the endocrinologist in the management of an operated case are at least twice as great as in a case not interfered with by surgery; in fact, the obstacles to complete restoration of health at times appear insurmountable. Many patients who have undergone one or more operations apply for medical aid and are found to have such marked degenerative changes in their vital organs that it is almost impossible for the internist to affect a cure. Careful nonsurgical management usually stops the progress of the disease even in this stage, but much of the damage to the vital organs cannot be repaired. It would be quite as reasonable to expect to cure patients with well pronounced nervous lesions from tertiary syphilis by means of antisiphilitic treatment.

The time has come when surgeons and internists must discriminate between "lumps on the neck." The division of thyroid enlargements into surgical and nonsurgical types, as pointed out in the chapter on classification of goiter, should be the first duty of the medical attendant confronted with the patient. An earnest endeavor so to classify goiter as to give rise to the least likelihood of unnecessary operations should and is in many quarters becoming a foremost medical topic. The pathological discrimination is important but insufficient, excepting in so far as it assists further to classify goiter into *surgical* and *nonsurgical* types.

Opinions of Other Clinicians.—Let us examine the views of other observers, both surgeons and internists, who are interested in this field:

André Crotti: "One may think the distinction between these two forms of goiter devoid of interest. Therein lies the mistake, for the distinction between them is of great clinical and prognostic value. The thyrotoxic nodular colloid adenoma responds to surgical treatment far more readily and safely than the parenchymatous one." In other words, toxic adenoma is a relatively safe surgical risk, but in the thyroid swelling of Graves' disease surgical interference is replete with disaster. We heartily agree with Dr. Crotti. Again, the same author remarks: "As a general principle, in exophthalmic goiter surgery it is better to err in favor of conservatism, and when in doubt, it is by far safer to ligate than to thyroidectomize, and to resort to two ligations instead of three, one instead of two. It is better to have an imperfect result than it is to have death, inasmuch as the first alternative may be remedied by a subsequent operation, whereas the

latter is beyond one's reach. . . . The *early mild forms* of hyperthyroidism in young individuals *should be treated medically*. We often see young women in schools and colleges, girls and débutantes react to overwork and undue excitement with a mild form of hyperthyroidism. They complain of nervousness, palpitation, insomnia, loss of appetite, muscular asthenia; the cardiac action runs up to 100 or higher; they have a moderate thyroid hyperplasia. This class of patients should be the triumph of medical treatment. Such patients should be treated with rest in bed for several weeks or months until the condition has subsided. Furthermore, their activities should be stopped and complete relaxation obtained. Here all physical as well as medicinal means which medical treatment possesses can be applied."

Emil Goetsch: "Single lobectomy does not give such rapid recoveries but is safer, whereas one can expect marked improvement to cures within three to six months after double resection. After single resection it may require a year or two before relief from symptoms is obtained. However, after a period of three to five years it seems that results from a single lobectomy are as good as those from a double lobectomy." This is a frank admission of the *absence* of the spectacular prompt results often claimed by surgery. Properly applied *nonsurgical* measures requires much less than a period of three to five years to accomplish complete recovery.

Charles H. Frazier: "How little is known today of the function of the thyroid even though surgeons have been removing them by the thousand! How many physicians still question the propriety of operating for toxic goiter and assume a skeptical attitude as to the reported results of surgical interference! It is my own belief that the present status of surgical therapy is but a stepping stone to the development of some method of arresting the toxic functional disturbances of the gland, and that eventually other measures, perhaps nonoperative, will be forthcoming, that will deal with the cause rather than the effect of deranged function and by removing the cause, break the vicious circle." Again, ". . . I do not mean to infer that the management of the toxic goiter belongs solely to the domain of the surgeon. The instances of favorable response to therapy other than surgical are too numerous to warrant such an assumption. Furthermore, I would not want to be understood for a moment as an advocate only of surgical therapy. In fact, I cling to the belief that when the chemist reveals to us the activating agent, which causes the characteristic hyperplasia of the toxic goiter, the missing link in the chain of scientific facts, a remedy may be found which will arrest the hyperplasia and render the gross removal of the diseased gland unnecessary." And elsewhere Frazier remarks, "A residual tachycardia may persist for weeks or the pulse rate may never return to normal, the exophthalmos may not disappear without a secondary operation, but the patient regards his condition with abso-

lute satisfaction." This statement, at least on its surface, is somewhat inconsistent. How can a person whose pulse rate has never returned to normal regard his condition with absolute satisfaction? An abnormal pulse rate is incompatible with a return to normal usefulness.

E. McD. Stanton, in a study based on the analysis of some 1,600 cases found in literature, arrives at these conclusions: "Removal of a portion of the thyroid gland of patients suffering with exophthalmic goiter produces a profound immediate effect noticeable within a few days of the operation and characterized chiefly by an improvement in the subjective symptoms of discomfort felt by the patient, but also accompanied by a marked fall in the pulse rate, a diminution of the tremor and an increase in weight. *This initial improvement, however, seldom amounts to a cure.*¹ The exophthalmos usually persists for months or years. The heart remains irritable, the pulse becoming rapid with exertion or excitement, and at irregular periods we may expect acute exacerbations of toxic symptoms, which may alarm both the patient and the surgeon."

J. T. Mason, of Seattle, commenting on "Mistakes Made in One Hundred Thyroidectomies" remarks: "Ligation will often precipitate a severe attack of hyperthyroidism. There is always a reaction; this is especially true following ligation. The collateral circulation is unquestionably restored within a few days. . . ." The probability is that to the shock of the ligation there is added a collateral circulation which not only compensates but frequently overcompensates Nature's desires for thyroid vascularization.

C. Capezzuolo, in a review of the literature on the results of operative treatment of exophthalmic goiter, including his own experience, states that surgeons might find, on examination of patients sometime after operation, many patients relapsed who had been reported as cured. Though a surgeon, this author insists that a course of medical measures should be tried repeatedly.

"*Dr. Crile* some years ago made the statement in reference to cases of hyperthyroidism (with exophthalmic goiter or not) that he thought it necessary after thyroideectomy that the patient be sent to a convalescent home in the country for six months if cure was to be permanent. He then went to work to say that such patients made as great an improvement without thyroideectomy as did those who had been operated on."—Tom A. Williams.

J. F. Rice: "The opinion of an eminent surgeon that 90 percent. of all goiters can be so improved by medical treatment as to make operation unnecessary was probably based upon observation of the effect of rest, for rest is the common element in all the various forms of treatment that have proved successful. (That opinion, by the way, is Kocher's endorsed by Chas. H. Mayo.)"

¹ Italics are mine.

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Carrington Williams: "Group III (exophthalmic goiter) are improved by surgical treatment; the prognosis, however, is not comparable to what may be expected in Group II (toxic adenoma). We believe that the best results claimed in treating exophthalmic goiter have been due to operations on cases in Group II which is not exophthalmic goiter. The converse, however, is true—that is, that poor results are in cases which we would classify in Group III."

W. H. C. Romanis states that thyroidectomy improves but does not cure the patient. Though there is an increase in weight, a lowering of pulse rate, and an improvement in the heart action, the pulse rate does not reach normal, the heart is still dilated, and the eyes still present exophthalmos. Even multiple operations do not produce complete cure.

Dean Lewis: "We are beginning to realize that all the ductless glands are intimately related and that in cases of ductless gland disarrangement we are dealing with a pluriglandular syndrome. We can expect ideal results when we can bring about a readjustment of these glands. At present we are not doing this, as would seem to be indicated by the frequency with which some syndromes persist even after most successful thyroidectomy."

James Berry states that his experience leads him to a less sanguine view of the advantages of operation on patients with Graves' disease, because of the tendency to relapse even after the most successful thyroidectomy and the incompleteness of the cure in many cases that at first sight seem most favorable. Even when performed under the best of conditions, the removal of a hyperplastic goiter involves considerable danger to life—far greater than that of operations for simple goiter. The mortality is at least 3 to 5 percent., and in many quarters it is far higher. Many patients who had made apparent recovery from the operation and were practically well for a considerable time may relapse or even die of the disease. In some of these a second operation is advisable, but there is a limit to the amount of gland that can be removed, lest the ultimate condition of the patient may be as bad or even worse than the first.

C. F. Hoover: "I have been unable to see any justification for amputation of part of the thyroid gland as a direct treatment for Graves' disease."

Russell, Millet and Bowen: ". . . Although both Goetsch and Woodbury claim clinical improvement in almost all their cases following thyroidectomy, in no instance had their patients been followed over a period of nine months. Furthermore, we do not feel that the degree of subjective improvement reported is sufficiently striking, in the absence of careful control by direct personal observation and the repeated use of function tests, to justify any dogmatic statement on this most important point. Particularly is this true since the psychological effect of operation and the recognized value of a subsequent rest period might

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together be sufficient to produce a definite, if temporary, amelioration of symptoms. We must not be unmindful of the danger of hypothyroidism developing in these cases as a result of thyroidectomy. As far as we know no report has yet been published of basal metabolism estimations following these operations."

W. V. P. Garretson: "The extirpation of a hyperactive thyroid gland is in most instances absolutely contraindicated and is a procedure based upon ignorance of glandular function. The gland is overactive in an effort to compensate for a deficiency of function elsewhere in the endocrine gland chain. The intimate interrelationship of glandular function teaches us that hyperactivity is a compensatory effort to offset hypoactivity elsewhere."

A. J. Walton aptly remarks that the surgeon does not see the medical successes because he is not brought in contact with them.

David Marine: ". . . We must look for the essential cause of exophthalmic goiter outside the thyroid. . . . From the standpoint of pathologic physiology, this overactivity of the thyroid seems primarily a purposeful or compensatory reaction due either to the exhaustion or partial loss of the regulatory control over oxidation processes normally exercised through the sympathetic nervous system."

Leonard Williams states that operations on the thyroid gland are inadmissible in Graves' disease. The disease is not only not a hyperthyroidism, but is not a disease of the thyroid gland at all. Many patients with advanced stages of the affection present no enlargement of the organ. Graves' disease is a toxemia in which all the members of the endocrine family are involved. There is no more justification for the removal of a lobe of the thyroid in Graves' disease than there is for the removal of one kidney in diabetes.

S. P. Beebe: "The present low mortality of thyroid surgery in competent hands has been obtained at the cost of many unfortunate victims as a rule."

Lewellys Barker: ". . . It must be remembered, however, that even after surgical operation upon the thyroid gland, patients who have had Graves' disease with diffuse hyperplastic goiter rarely regain perfect health. They require close medical supervision for a long time, often for the whole of life. . . ."

J. B. Dieulafoy (quoted by Haeberlin): "It is . . . impossible at present to give surgical treatment the preference over medical means."

F. B. Scott: "That brilliant craftsman, the thyroidectomist, should become an anachronism, a tradition only of the dark days that are gone; and medicine, strong in physiological and philosophical faith, should resume her peaceful sway."

J. M. Pearson: ". . . Strictly speaking, he (the surgeon) in the last event, does not cure the patient. To take away an offending portion of the body can in no sense of the word be considered the equivalent

of restoring its integrity or causing the peccant portion to resume its orderly function."

Solomon Solis-Cohen: "In Volume LXV (1911) of Guy's Hospital Reports, Dr. Hale White records the results of an attempt upon his part to trace the history of patients discharged after medical management during the last twenty years, and he finds that in about 80 percent. the recovery has been permanent. In my own personal and consultation practice I have had the opportunity to observe a number of patients for periods varying from a few months to twenty-five years after apparent recovery from nonsurgical treatment. In but one instance has there been relapse, and in no case had death occurred from any condition with which Graves' disorder could be causatively associated."

T. R. Dunhill, in a recent symposium in London, stated that he never operates on a patient with Graves' disease without fear and great anxiety, a feeling which does not leave him until some days after the operation.

Robert McCarrison: "The practice of operative interference with the thyroid gland in all cases of Graves' disease at sight and without applying all our resources of our art in the detection of its cause, as is now a very common custom, is one which cannot be too strongly deprecated. I am convinced that . . . the number of cases in which thyroidectomy is performed will become smaller and smaller and its practice except in cases which have baffled the most painstaking investigation, will ultimately be abandoned."

And so we may quote innumerable internists and surgeons who are entirely dissatisfied with the end results of surgery in exophthalmic goiter, despite the low mortality rate and neat scars. They are convinced that the *rationale* of surgery is entirely wrong; that the cause of the disease is not effaced in this fashion; that not only is the patient not cured by surgery, but a deficiency of natural defense is an added factor in a thyroidectomized patient; and lastly, internists and surgeons throughout the world are convinced that thyroidectomy in Graves' disease has filled more graveyards than total resignation of those patients to the course of the disease.

What the Thyroid Means to Us.—"The thyroid is not essential to life, but it is synonymous with making life worth living."—George W. Crile. If this be true, then the surgical removal of five-sixths of the organ deprives the patient of five-sixths of that which is responsible for making life worth living. This is especially true of the aged, who require the entire thyroid gland to avoid becoming subjects of myxedema. The claim that the patient can get along with one-fifth or one-sixth of the thyroid tissues originally given him by Nature is fallacious. Though this may appear to be true during sleep and during moments of wakefulness akin to sleep when body and mind are at a low ebb of activity, and are, so to speak, hibernating, a normally active individual requires

all his thyroid structure and function in order successfully to compete physically and mentally with his fellow men. If we were endowed with a kind of supernatural vision, we would see the thyroid serving as a physiological barometer, indicating every physical and mental stress essential to the onward march of civilization. Not only are patients with lessened thyroid substance unequal to normal physical and mental demands, but since this organ plays an important rôle in immunizing



FIG. 151.—Post-operative Graves' syndrome in a man of 48. Thyroidectomy was performed despite the fact that the patient's thyroid was never swollen. This picture was taken 7 years after operation. Patient had been confined to his room for many months; there was marked cardiac dilatation and auricular fibrillation with heart rate of over 200 and pulse deficit between 60 and 70; there was moderate exophthalmos, extreme weakness and sweating, marked tremor, loss in weight, and a persistent premonition of impending death. Basal metabolism plus 68.



FIG. 152.—Same patient as in Fig 151 after 7 months of treatment as outlined in this volume. Heart area restored to normal limits; heart action regular and rhythmical with a rate of 70 per minute; eyes normal; there is a gain of 25 pounds in weight; basal metabolism is plus 4. The patient is now experiencing unprecedented health and has returned to his business.

processes of the body, a person possessing but a fraction of his thyroid is especially prone to infection. Cobb has well said that the position of the gland in this disorder has been recognized to be that of an organ more sinned against than sinning. In fact, the thyroid now receives credit for its attempt to stand between toxemia and the functions of the body; its reward being, in many instances, to be robbed of half its territory by the surgeon's knife.

The Solution of the Problem.—In the management of Graves' dis-

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ease, the etiology of which is as elusive as the fountain of youth, the symptomatology of which is as varied as the colors of the rainbow, with a syndrome seemingly characterized by more vicious circles than are seen elsewhere in the domain of medicine, in brief, in a disease presenting so great a confusion of structural, functional and psychic features for study that the keener the observer, the greater the problems still unsolved—is it any wonder that the patient is a burden to the general practitioner? Is it to be marvelled at that the busy general practitioner, finding himself incapable of managing his charge, and unacquainted with an internist especially trained and skilled in this work turns the "case" over to the surgeon? Heretofore, both the surgeon and internist have shown a tendency to expect *immediate* results and to draw their deductions and statistics from measures according to whether or not *prompt* improvement was manifested. Distal permanent results and complete recovery were forgotten in the haste for a quick, though temporary reduction in pulse rate and basal metabolism, and when "cases" were followed up, the statement of the patient, through the mail was accepted as reliable. Personal contact with the patient for a year or two was unusual, and when this occurred results were not as expected. Information was lacking from patients in a state of extreme invalidism, those suffering with myxedema and those dead of the disease.

Surgeons should show less haste and internists more patience in the management of these unfortunates. Though hopeful, the general practitioner does not expect cure through the surgeon's efforts—his present experience based upon previous instances teaches him that the most to be awaited from surgical effort is temporary improvement. But he is perforce thankful even for this, as the responsibility for holding on to such a patient is great.

In a discussion following the reading of a paper in Brooklyn, a prominent thyroid surgeon¹ rightfully asked: "If nonsurgical measures are universally productive of cures, why do they come to *us* for operation? If all medical men could demonstrate the results shown by Dr. Bram, we would not have so many cases for operation." In responding to this query and remark, there was but one thing to say, and that is, that there is a lack of interest, of enthusiasm and of energy displayed by the general practitioner in his attitude toward the study of his cases of Graves' disease. When medical men will devote more time in an effort to delve into causal relationships in etiology and individualization in the therapeusis of the affection, the results will become uniformly good, and surgeons, realizing this, will turn their patients over to the internist. *It is the dormant attitude of medical men in general that is responsible for thyroidectomies in Graves' disease.*

¹ Emil Goetsch in discussion following my lecture on "The Heart in Graves' Disease," before the Brooklyn Cardiological Society, November 27th, 1922.

It is not clinical cure that gives to surgery its present position in the therapeusis of exophthalmic goiter; it is its lowered *operative mortality* and the scarcity of understanding internists. This is an age of particularization. Specialization is still in the making, is still seeking to eliminate the term "incurable" from the vocabulary of the medical profession. Exophthalmic goiter is quantitatively and qualitatively as difficult a subject, presenting problems as many and as grave, requiring as much training and skill, as any specialty extant. With the development of a sufficient number of such clinicians, scientists capable of ferreting out all predisposing and exciting etiological elements in a given subject of Graves' disease, irrespective of the time and pains involved,—who can apply the necessary remedial measures whether they be prophylactic, dietetic, hygienic, medicinal, electrotherapeutic, psychotherapeutic, in appropriate combination as indicated, after a careful individualizing analysis—in brief, with the appearance of an adequate number of internists who through years of patient observation, can virtually understand and speak the language of subjects of Graves' disease, there will be a cessation of surgical interference in this affection. Exophthalmic goiter will then cease to be the dread disease that it now is, and recovery will be but a matter of time.

Percentage of Nonsurgical Recoveries.—Does nonsurgical treatment of exophthalmic goiter yield one hundred per cent of cures? There are three classes of patients who are obviously unsatisfactory: (1) Those who are evidently moribund; (2) those who have developed a definite form of insanity, especially patients requiring physical restraint in order to overcome destructive tendencies; these patients are to be regarded as instances of mental aberration requiring chiefly the services of the psychiatrist; (3) those patients who, after several weeks of observation, are discovered to be noncooperative. I consider the first few weeks of treatment of any patient as probationary, and if, in spite of properly applied mental appeal, the patient is untruthful and otherwise unfair in obedience to orders, rather than court failure, I refuse further to treat him.

In brief, the properly equipped internist, after eliminating those who are moribund, the insane and the noncooperative, all of whom constitute approximately ten percent of patients who apply for treatment, should obtain one hundred percent of recoveries.

Surgery, unable to remove the cause of the affection, is a fallacious procedure. Nonsurgical measures,—the *rational* therapeusis of exophthalmic goiter, overcoming the dysfunction of the various structures and organs of the body and restoring the interglandular and neuroendocrine relationship, break up the various physical and mental vicious circles with consequent restoration to permanent health.

All things being equal, the prognosis of Graves' disease under nonoperative treatment is excellent; recovery is complete and perma-

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nent, and the patient, taught how to "carry on" and imbued with a healthy philosophy of life, becomes and remains stronger in body and mind than ever before.

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APPENDIX

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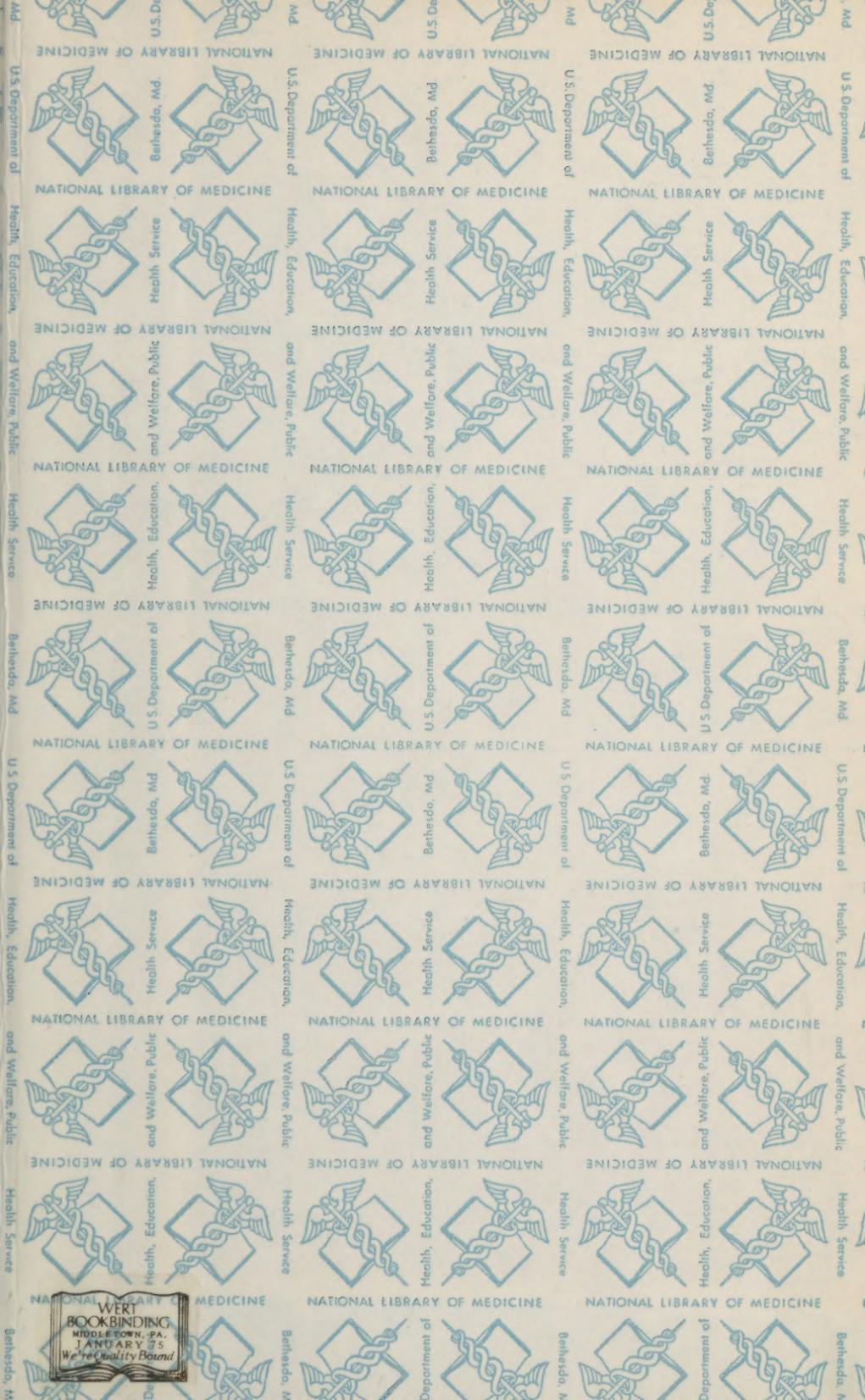
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